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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

SEPTEMBER 1939

SOME DIFFICULTIES IN THE USE OF THE INSULINS IN DIABETIC PRACTICE*

WALTER R. CAMPBELL

IN DISCUSSING the use of the insulins with an audience of practising physicians, it would seem advisable to confine attention largely to the products commercially available at present. Only two products, *Insulin* and *Protamine Zinc Insulin*, are licensed by the University of Toronto and accepted by the Council on Pharmacy and Chemistry of the American Medical Association at the present time. However, several other varieties of greater or less merit exist which may in the future supplant these.

Difficulties in the use of protamine zinc insulin arise in large measure from the fact that its properties have not been completely mastered, as well as from the fact that many physicians have failed to distinguish protamine insulin, which is still used in considerable amounts in Europe and was used in this part of the world in an experimental way for a short time, from the later product, protamine zinc insulin.

Numerous protamines exist and their combinations with insulin yield products with specific properties. Hagedorn first found that insulin

* Read February 10, 1939 at The New York Academy of Medicine, in the Friday Afternoon Lecture Series.

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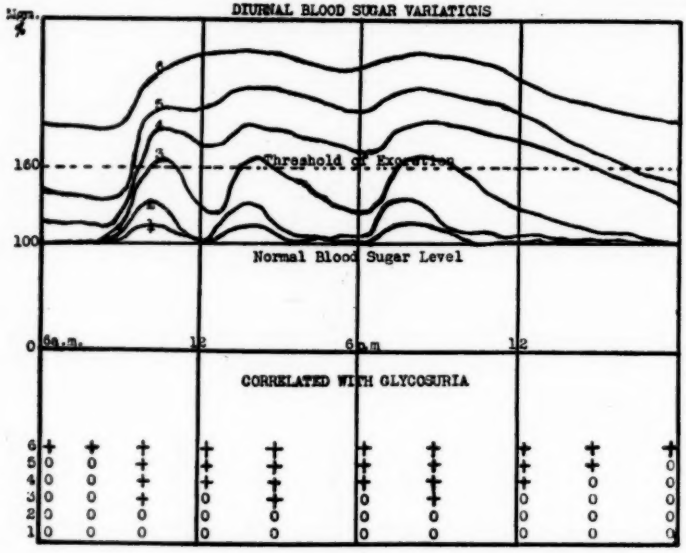

Chart I

combined with the protamine of the rainbow trout (*Salmo iridius*) had very desirable properties, a fact which was early confirmed by Joslin, Wilder and ourselves. But even more useful in certain respects was the insulin compound with king salmon protamine with which most of the experimental work on protamine insulin was carried out in America.

The investigations of Scott of the Connaught Laboratories, University of Toronto, showed a prolongation of action of insulin in animals by the addition of zinc and this we were likewise able to confirm in man, but the use of this product is accompanied by certain drawbacks. It became of great interest though to see whether or not the use of additional zinc might alter the properties of protamine insulin. Several new and very desirable properties were found to be possessed by this combination and it was made available commercially, under the name of protamine zinc insulin, as soon as adequate tests convinced us of its great value.

The first chart shows in a rather diagrammatic fashion the behavior of the blood sugar in normals and diabetics on an ordinary diet. In the normal individual there is a marked tendency to maintain the blood sugar level within certain definite limits. Nevertheless, following the

ingestion of meals, the blood sugar tends to rise somewhat for a short period and then to revert to a lower level within the normal band. Curves 1 and 2 are supposed to illustrate the fact that this is a variable phenomenon in different people. Seldom does the postprandial rise in normal individuals pass beyond .145 per cent. During the remainder of the twenty-four hours the blood sugar lies within the normal band. In other words, the normal variations in blood sugar do not pass beyond the level of the threshold of excretion, usually .160 per cent or a little higher, and no glycosuria results, as is indicated below. Glycosuria would result, however, if this threshold were lowered, producing the so-called renal glycosuria; and the greater the lowering of this threshold the more constant the glycosuria becomes. Occasionally this glycosuria cannot be stopped except by forcing the blood sugar to excessively low levels but, of course, this is never done as a practical measure of control. Renal glycosuria is a benign condition, an anomaly, requiring recognition rather than treatment. In Curve No. 3 we find the blood sugar starting within the normal values and rising after meals to overstep the threshold of excretion, glycosuria resulting at these times but disappearing as the blood sugar falls back to normal levels. This patient furnishes us with many problems. Numerous causes may produce this result: alimentary hyperglycemia, obesity, infection, liver disease, a lag type curve. But sometimes the patient is the mildest type of diabetic and peculiarly important because at this stage early strict treatment may wholly arrest the progress of the condition while he still has a high tolerance for carbohydrate or, perhaps, even bring about a cure. Curve 4 also starts within normal blood sugar limits but it rises above the threshold after a meal and continues thus, perhaps falling slightly before the next meal but rising again soon after this has been taken. After absorption of the evening meal the blood sugar falls to normal and remains so during the night. This patient is a mild diabetic, probably readily controllable by dietetic measures, but he introduces the question as to how much value he might gain from a period of support by a small supplement of a long acting insulin. Curve 5: Well marked fasting hyperglycemia with an increase above the threshold level after meals and long continued glycosuria, only ceasing during the night, is a stage of greater severity of diabetes, sometimes controllable by rigid dietary restrictions, and often benefited by small doses of insulin. In Curve 6 we have depicted the blood sugar level continuously above the

threshold level and constant glycosuria—a definite diabetic who will almost certainly require insulin to assist in metabolizing a suitable diet.

In connection with Chart I there are several points to be noted: a diabetic is not always continuously glycosuric; diabetes is not the most frequent cause of glycosuria; literally hundreds of other causes may operate but diabetes is the most constant and the most persistently recurrent cause of hyperglycemia and glycosuria as well as the probable cause of maximal deviations from normal values. Diabetes varies in severity. Besides other features which may often assist in diagnosis, both hyperglycemia and glycosuria either constant or persistently recurrent, are necessary for the diagnosis in most cases.

Chart II: All diabetics do not need insulin. When placed on restricted diet the mild diabetic promptly becomes sugar free. Some patients, however, become aglycosuric with greater difficulty and only after some days. Perhaps they may require insulin to assist in metabolizing more liberal diets required for their daily work. A third group will not become sugar free, and insulin definitely is necessary for these patients. A test period on restricted diet would eliminate many of those cases now placed unnecessarily on insulin and later found not to require it. I am not unmindful of the fact that in certain instances insulin administered to mild and early cases may sometimes be of value in ameliorating their severity, but on this subject too little data now exist. Their recognition is largely dependent upon adequate preliminary testing of their tolerance. In such a group with high initial tolerance there will be few difficulties to overcome in connection with the administration of insulin. One recognizes the greater stability of the normal individual to a given dose of insulin; these mild diabetics resemble normal individuals in this respect more than the severe cases of diabetes mellitus.

Reference to our early work on insulin will indicate that such insulins did possess a more prolonged action than the regular type now available commercially. Through the years, as purity of the product was increased, the action became more explosive, as it were, and an increasing number of doses was required to manage severe cases of diabetes. Whether the original long action was due to their high zinc content, which Scott has shown definitely prolongs the action of insulin, or to other adjuvants now refined out of the product, is not now known, but one may contrast the twenty-four hour action of early insulin, as shown in Chart III Curve 1, with the more rapid action of

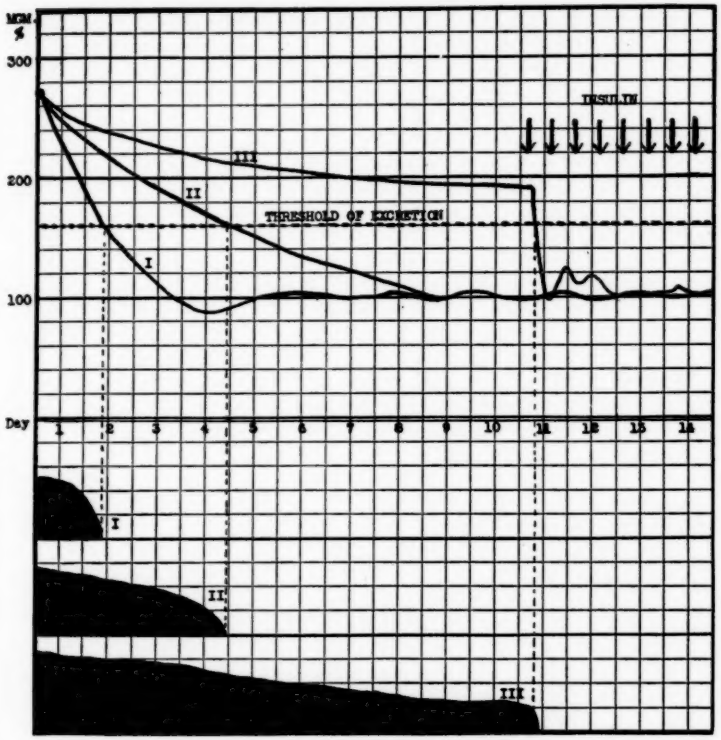

Chart II—Hyperglycemia and glycosuria in: I, mild; II, moderately severe; and III, severe diabetics under treatment.

1936 insulin in Curve 2. In the latter, the action is wholly completed before the older preparations had caused their maximum fall of blood sugar.

The third curve on Chart III shows the effect of an equal dose of Hagedorn's salmaridin protamine insulin in the same individuals. As will be noted, the action is more gentle and more prolonged than that of the unmodified preparation. Without doubt the modification of insulin by means of protamine and other substances has made possible the greatest improvement in diabetic treatment since the introduction of insulin itself.

How, then, does protamine zinc insulin differ from ordinary or unmodified insulin? I have endeavored to answer this in part in Chart

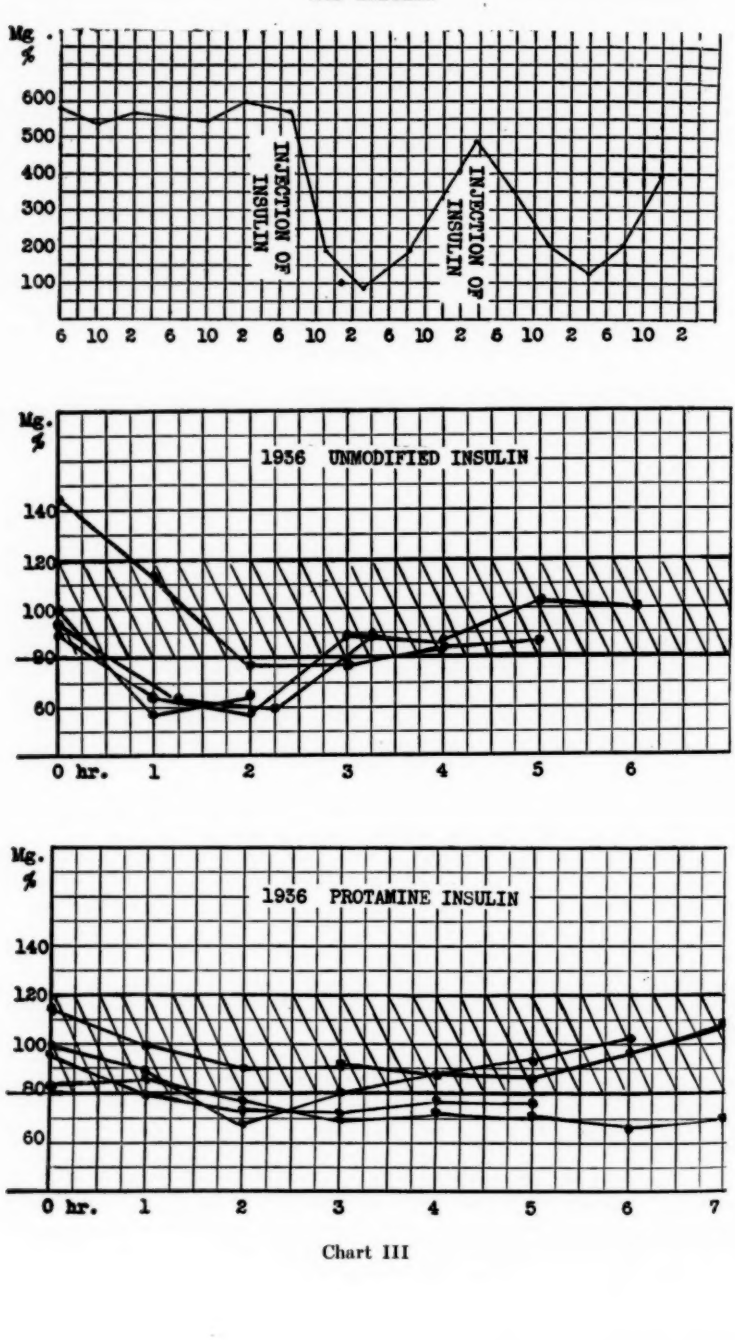
1922 INSULIN
Mg. %
600
500
400
300
200
100
INJECTION OF INSULIN
INJECTION OF INSULIN
6 10 2 6 10 2 6 10 2 6 10 2 6 10 2 6 10 2
Mg. %
1936 UNMODIFIED INSULIN
140
120
100
80
60
0 hr. 1 2 3 4 5 6
Mg. %
1936 PROTAMINE INSULIN
140
120
100
80
60
0 hr. 1 2 3 4 5 6 7

Chart III

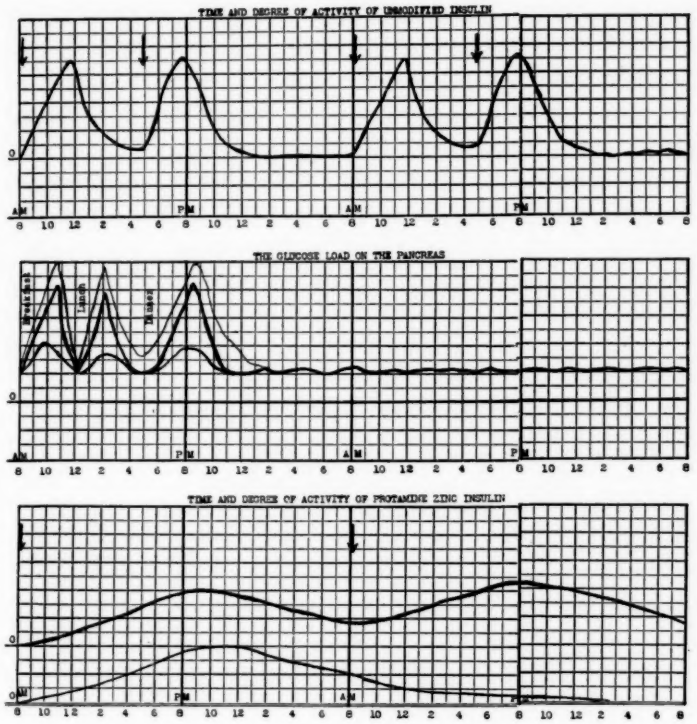

Chart IV

IV. Regular insulin is a solution and when injected is rapidly absorbed and available early to do its work but, as you will have noted previously, its action is now of short duration. If we allow the squares of Curve 1 to represent some hypothetical unit of efficiency, then the curve of insulin activity outlines the amount of work performed and we see that the diabetic given two doses of such an insulin in a day gets rapid large effect which is completed early, and during the night hours the patient is left dependent upon such insulin as he can produce himself. Quite probably, if the carbohydrate intake is not excessive, the pancreas supplies but little insulin during the period of action of the injected insulin and a greater amount of the patient's own insulin is available for the night hours. It is also true that during fasting or during the night a comparatively small amount of insulin is required but the relatively small store of glycogen soon is used up. The patient falls back on

protein utilization to obtain the necessary energy to live and by morning the blood sugar of the patient rises to abnormal levels unless suitable further injections are introduced or unless the patient has sufficient insulin production of his own to counteract this process. In other words, in the case of patients with small insulin production or patients on high calory or high carbohydrate diets with unmodified insulin, the diabetic tendency is mastered for only a few hours of the day; the remainder of the time he is only a little less diabetic than before. Particularly is this true of patients who are allowed to have high blood sugar or a little glycosuria as often has been done, allegedly to protect them from the dangers of nocturnal reactions.

Before contrasting these effects with those of protamine zinc insulin, we may examine Curve 2, which represents what I conceive to be the normal distribution of the glucose load on the pancreas, meaning by this not only the absorbed carbohydrate as such but also that derived from the glycerine of fat and the breaking down of protein. The starting point of the curve, being somewhat above the zero line, is intended to represent the fact that some insulin is required normally for endogenous metabolism even during fasting. However, immediately the carbohydrates from the meals commence to be absorbed, this load is increased in degrees varying with the amount absorbed. Following the absorption of food the load falls to a lower level which persists throughout the night. Now, comparing this curve with Curve 1, we see that regular insulin is most usefully employed to counteract the effect of the ingested carbohydrate. The more effectively these two factors are balanced, the better the patient's own insulin can be used to maintain a normal state during the night. In many cases this has been found to be actually insufficient and small supplementary doses are required to keep the patient normal during this period. It is apparent, then, that a longer acting insulin would be desirable to reduce the number of doses of insulin required and to maintain the normal metabolism of the patient for a longer period of time.

Salmaridin protamine insulin provided a partial answer to these requirements, being effective in maintaining normal metabolism for some sixteen hours. Onchorhynchin protamine insulin was effective for some twenty-two hours. Chart III indicates that the zinc modification of onchorhynchin protamine insulin has a still longer effect. Taking the lower line, the curve indicates that, though the slow absorption of the

suspension of this product makes a high degree of activity impossible, the activity is continued in useful amounts for some thirty hours. Indeed, Wilder has shown that some activity is present for fifty-seven hours; similarly my colleague, Dr. Fletcher, has obtained evidence that a minimal degree of activity persists for some sixty hours during partial fasting. The upper curve represents the fact that the effect of successive daily doses of protamine zinc insulin is cumulative to some degree. Yesterday morning's insulin helps to provide in part for the metabolism of today's breakfast.

Comparing the action of this insulin with the glucose load on the pancreas, Curve 2 indicates that it will be most effective in balancing the constant load of the endogenous metabolism on the insulin-producing mechanism rather than in ironing out the peaks in the curve induced by the absorption of food. *The maximal useful dose of protamine zinc insulin is that which leaves the patient with a low normal fasting blood sugar without nocturnal hypoglycemia.* By this means he attains the largest margin between the fasting blood sugar level and the threshold of excretion after breakfast, and somewhat better rest for the pancreas during the night so that any self-manufactured insulin may be devoted to controlling the absorptive hyperglycemia. Possibly this rest accounts also for the slow reduction in insulin requirement noted in so many cases. As the new injection of insulin is gradually absorbed and reaches its maximum level, larger amounts of carbohydrates may be placed in the later meals of the day. However, protamine zinc insulin alone is ill adapted to the consumption of high carbohydrate diet and any hyperglycemia or glycosuria encountered is very slowly controlled. One may attempt to counteract this, as well as the tendency to nocturnal hypoglycemia because of overdosage of insulin, by putting a portion of the carbohydrates into a bedtime lunch, but this procedure is not entirely satisfactory. Prolonging the digestive and absorptive period by suitable selection of food may lower the peak of the load and permit the use of 5 to 8 units of more long-acting insulin. This may be done in suitable cases by using unripe bananas, by smothering berries or peaches with cream, by using heavy cream or butter on oatmeal or puffed cereals, by using fat meats, French-fried potatoes and French sticks or Vienna rolls liberally spread with butter. With long-acting insulin the problem of evening refreshments can be solved safely by taking a supper somewhat lower in carbohydrate than usual and selecting suitable refresh-

ments. One of my patients, whose severe diabetes remains unknown to his associates for business reasons, has made himself popular with hostesses by his activities in serving the evening refreshments. No one ever notices that he has no time to eat more than a small sandwich, a few nuts, or drink a cup of coffee. If it appears necessary to take more, he walks home "to clear his head of the smoke." The walk uses up a little more carbohydrate. He has never had glycosuria or hypoglycemia since going on protamine zinc insulin nearly three years ago.

It must be clear that protamine zinc insulin has but a limited capacity to take care of ingested carbohydrate and that treatment is more successful with the lower carbohydrate diets than with those containing a more liberal amount. Roughly, it may be said that severe diabetics cannot take a diet exceeding 100 grams of carbohydrate (or 150 grams total glucose) while using a single morning dose of protamine zinc insulin. An attempt to do so results in glycosuria, hypoglycemia or both. With diabetes of lesser severity a larger amount of carbohydrate can be utilized by giving the protamine zinc insulin in amounts sufficient to produce a low normal fasting blood sugar without hypoglycemia and utilizing the remaining pancreatic efficiency to counteract the postprandial hyperglycemia and glycosuria. Successful treatment, according to my criteria—adequate caloric intake and maintenance of the blood sugar within normal limits—becomes more and more difficult to attain as the carbohydrate in the diet rises, but sometimes is accomplished if the total calories can be kept low. Amounts of carbohydrate much above 150 grams, in my opinion, are usually unwise unless it is necessary to provide more because of failure of lipase secretion by the pancreas. Many patients on diets containing 250 grams of carbohydrate would be better on a lower carbohydrate ration without insulin.

In the fasting state the slowly absorbed insulin is definitely more economical than regular insulin. Fewer units are required and in addition hypoglycemia is not so much to be feared. If calories are allowed at a working level, this economy diminishes as carbohydrate in the diet increases. When the carbohydrate of the diet is below 100 grams, 60 per cent as much protamine zinc insulin as regular insulin will be equally effective. At 100 to 125 grams of carbohydrate, 75 per cent as much protamine zinc insulin as regular insulin will be required. But little economy is observed when more than 150 grams of carbohydrate are given in a working diet. On the other hand, if undernutrition diets are

prescribed, considerable economy is observed with somewhat larger carbohydrate allowances.

To many, the plan of giving protamine zinc insulin in small and gradually increasing doses from the beginning of treatment commends itself, especially if ambulatory treatment is necessary. There are numerous advantages in commencing treatment under hospital conditions, however. In this case it seems preferable to determine whether the patient can metabolize a basal diet and then increase the food allowance in ladder fashion towards the maintenance level, using regular insulin, if necessary, as the required period of observation is far shorter than if protamine zinc insulin is used. In transferring patients from regular insulin to protamine zinc insulin, doses up to 75 units per day of the unmodified insulin are substituted by 60 per cent as much protamine zinc insulin given in a single morning dose. However, since the insulin from this injection is absorbed slowly, it is probable that glycosuria may occur prior to the insulin becoming available. To obviate this, 60 per cent of the balance of the original dose of regular insulin is given with the first dose of protamine zinc insulin and the remainder of the regular insulin before the evening meal. On the following day, the morning dose of protamine zinc insulin is accompanied again by regular insulin, as before, but thereafter it is discontinued.

If a patient attains a low normal fasting blood sugar level without nocturnal hypoglycemia on a given dietary regime, but shows glycosuria, examination of urine collected every two hours is indicated to determine the time of the glycosuria. Onset of glycosuria, not duration, is the more important, though large increases in glycosuria following the later meals are also significant. Not infrequently some rearrangement of amounts of carbohydrate in the various meals may cause the glycosuria to disappear. Spreading the meals over a larger number of hours or smothering the carbohydrate in fat, as suggested by Pollack, may be tried, or even a bedtime lunch which may make possible a few more units of insulin without inducing hypoglycemia. Should these measures fail, one is faced with the alternative of using less carbohydrate in the diet or of reinforcing the action of the protamine zinc insulin and of the pancreas with some regular insulin. With severe diabetics reinforcing with regular insulin nearly always will be required, as also is usually the case when very high carbohydrate allowances are made without shrinking the total calories. Regular insulin should be adminis-

tered in addition to the previous dose of protamine zinc insulin at first, though later it is probable that the protamine zinc insulin may be reduced somewhat. Preferably, regular insulin should be given in the morning, close to breakfast time, and it is most convenient to give the protamine zinc insulin at the same time. With protamine zinc insulin, as opposed to the more rapidly acting protamine insulin, there is comparatively little to be gained by shifting the time of injection by one or two hours, so that giving it with the breakfast does not matter except as a minor inconvenience to the patient.

Attention should be called to a detail which sometimes is neglected. Adjustment of the insulins to the requirement of the resting individual is frequently not the most satisfactory for the working individual. The perfectly adjusted hospital patient frequently has difficulty with hypoglycemia on his return to working conditions. I feel that there is little doubt that gradual increases in the diet to a working level give the most satisfactory results in treating the diabetic but, in approaching the working level of the diet from below, it is desirable to arrange increases in activity, such as walks or occupational therapy, to simulate the working conditions of the patient and thus avoid abrupt alteration of conditions on discharge from hospital. A little more attention to this point would avoid many of the difficulties and disappointments now being experienced with protamine zinc insulin.

An occasional cause of glycosuria and, later, hypoglycemia may be the failure of the patient to observe the caution to mix thoroughly the suspension of protamine zinc insulin in the bottle before removing the dose. Neither insulin should ever be injected intramuscularly because of the injury to muscle tissue, and protamine zinc insulin should not be injected intravenously as most of the prolonged effect is lost and the patient is subjected to a certain amount of danger from the protamine itself.

It may not be amiss to point out here that when we were working with protamine insulin I introduced the method of layering the two insulins in the same syringe and injecting them through one skin puncture in two places under the skin. This was a convenience but is not possible with protamine zinc insulin. For stabilization purposes, protamine zinc insulin contains both excess protamine and excess zinc so that, if mixed in the tissues, all will become protamine zinc insulin. However, it is still possible to avoid the pain of a second skin puncture

by using three-quarter inch needles and two syringes. A needle is attached to the syringe containing regular insulin, plunged far, but not deeply, under the skin and the contents injected; the needle is almost withdrawn, its direction changed, and again inserted to a point some distance from the original injection; the empty syringe is now removed, a syringe containing protamine zinc insulin substituted and its contents injected.

The more severe the diabetes, and the higher the carbohydrate content of the diet, the more likelihood there is that more than one daily dose of insulin will be required. In my experience, when more than 50 units of protamine zinc insulin are required, it is comparatively seldom that the long acting insulin alone will adequately control the patient's metabolism. In such instances the change-over morning dose of regular insulin, mentioned above, may be continued and usually it will be found advisable within the next few days to reduce the protamine zinc insulin to 50 per cent of the amount of regular insulin originally used. No absolute rule can be laid down, however, since results are so much dependent upon the original tolerance of the individual, the total calories and the proportion of the diet made up of carbohydrate substances. The useful dose of protamine zinc insulin is limited by the production of nocturnal hypoglycemia. This must be avoided. At the same time, it is desirable to use sufficient protamine zinc insulin to ensure a low normal fasting blood sugar in the morning. From this basis the appropriate amount of regular insulin may be worked out by watching the postprandial hyperglycemia and glycosuria. Experiments have been made giving the protamine zinc insulin at various times of the day, and sometimes these are successful. Administration of protamine zinc insulin at eleven o'clock at night, so that its maximal action occurs around breakfast time in the morning, occasionally has some advantages. However, it frequently results in hypoglycemia before breakfast. Administration of two smaller doses, morning and evening, may result in utilization of more carbohydrate although it does away with the convenience of a single injection. With some few patients it may be necessary to give protamine zinc insulin in the morning together with regular insulin, and to administer a second dose of regular insulin later in the day in order to keep the patient free of glycosuria. In these cases I have noticed that this usually is a temporary requirement and that later, presumably because of the benefits of rest to the pancreas, the evening dose can be

discontinued. Of course, the state one wishes to attain is that of an adequate diet with a normal blood sugar throughout the twenty-four hours; a considerable amount of experimentation, both with dietary regimens and insulin dosage, is sometimes required to attain this in instances of maximal severity. The twenty-four hour blood sugar curve, though much used by us, is not necessary for routine treatment. A low normal fasting blood sugar, a blood sugar of .145 or below at 10:30 A.M. and freedom from glycosuria or hypoglycemia throughout the day will ensure that no gross deviations occur.

In no case is the abandonment of protamine zinc justified by its failure to do what it may legitimately be expected to do if its powers and limitations are fully understood. The trouble lies with the lack of knowledge or therapeutic resource of the physician or with what one may call the idiosyncrasies of the patient. The latter, of course, cannot be left out of consideration, but the ultimate benefits to be derived from protamine zinc insulin alone, or in combination with regular insulin, are worth considerable study in every case.

I suppose everyone would desire an amelioration of the dietary restrictions of the diabetic. In this connection the considerable advantage of being able to combine in one solution a rapidly acting insulin and a more slowly acting factor, capable at once of combating absorptive hyperglycemia and of controlling the endogenous carbohydrate metabolism of the body apart from meals, has not escaped notice. Numerous experiments have been made with this object in view but, unfortunately, I can give you no idea when such a product may become available. Work of this sort is time-consuming and many failures are to be expected before the adequate solution is attained.

The effect of infections on the patient using protamine zinc insulin is somewhat variable. We believe that thorough treatment of diabetics tends to raise their resistance to infections toward the normal and so lower the incidence of infections which become of clinical importance. With regular insulin it is well known, however, that in severe infection the usefulness of the insulin is materially diminished and non-recognition of this fact may be responsible for development of acidosis and even of coma in these patients. With protamine zinc insulin the rate of absorption of the insulin and the rate of action is much slower and toxic effect on insulin efficiency, however it is brought about, is decidedly more marked. As part of their training, diabetic patients should be

warned to consult their physician immediately upon the development of any infection and appearance of either glycosuria or ketonuria. In treating these patients I prefer to leave the dose of protamine zinc insulin unchanged and add regular insulin in small, frequent doses to supplement its effect, reducing the unmodified insulin dose, of course, as the need for it subsides. In initiating diabetic treatment in a patient with an infection, one would prefer the use of regular insulin for its more rapid effects. As an adjunct to regular insulin, however, some use what may be called a sustaining dose of protamine zinc insulin and believe it to be of benefit to the patient.

There is some conflict of opinion on the use of protamine zinc insulin in relation to surgical operation. Some prefer it to regular insulin. If the patient already is using protamine zinc insulin, I would not discontinue it but would supplement the dose with regular insulin and glucose preoperatively, watch for evidence of acidosis following operation and, if necessary, use supplementary doses of regular insulin to combat it. Diabetics not requiring daily insulin otherwise should receive regular insulin and carbohydrate before operation unless their carbohydrate tolerance is high. Postoperatively, a sustaining dose of protamine zinc insulin is hardly necessary and, in order to avoid a later hypoglycemia, is inadvisable unless glucose is being administered intravenously at the same time. For an emergency operation because of infection protamine zinc insulin is useless, being too slow in its immediate effects. There is, possibly, something to be said for a sustaining dose administered before operation for use in the postoperative period, when glucose is being administered intravenously but, as an emergency due to the toxic factor destroying the insulin must be met with regular insulin in any case, I prefer to avoid the complicating factor and use regular insulin alone.

Acidosis in the diabetic patient is still too frequent. As a complication of infection it probably occurs more often in the patients treated with protamine zinc insulin than in those treated with regular insulin. It should be treated by adding regular insulin to the protamine zinc insulin treatment. When induced by neglect of treatment, or improper dietary control, the quickest way to bring it under control is by the use of regular insulin. Should an occasion arise when it is desirable to control a mild acidosis without creating alarm, orange juice and other fluids and liberal doses of protamine zinc insulin probably will be effective and

may be reinforced by regular insulin at any time, if necessary. Protamine zinc insulin will do the work if time is available. However, it is not always wise to allay the alarm of the careless patient and his neglectful relatives.

Coma is an emergency and should be treated as such. Today patients die, not of coma, but of the circulatory failure induced by coma. Properly treated with large doses of regular insulin, they should be out of coma before any considerable effect could be expected from protamine zinc insulin. To smooth the course of the immediate after-treatment and to prevent protein breakdown between periods of activity of the regular insulin, a dose of protamine zinc insulin administered early might serve a useful purpose. But if sufficient regular insulin is being used to ensure maximal conversion of metabolism to a carbohydrate type, it is difficult to imagine any occasion for its employment.

When Fletcher and I first described the clinical syndrome hypoglycemia, we felt it of the utmost importance to impress on those using insulin the dangers of the new drug. Insulin hypoglycemia is still dangerous but, in most instances, not to the degree we had anticipated. Today, insulin hypoglycemia, when induced by protamine zinc insulin, is dangerous in comparison with regular insulin, but the number of reactions is cut down materially. The danger lies partly in the insidious onset of hypoglycemia and in the tendency to recur when once cured with soluble carbohydrate. The older symptoms were associated with speed in the fall of the blood sugar; the newer insulin often steals away the blood sugar so gradually as to excite almost no symptoms until severe reaction levels are attained. Also, even with the immediate reaction cured, the remaining unabsorbed insulin on entering the blood stream may cause repetition of the reaction some hours later. While the well-known symptoms are encountered in some cases, hypoglycemia with the new insulin is often accompanied by a sensation of undue fatigue, negativism, slight headache or nausea and evidences that the normal repressions are lacking. Signs of deficient cerebral control, as in mild alcoholic intoxication, are more prominent features of the new picture. Somewhat greater difficulty is experienced in controlling reactions which have progressed to this blood sugar level but soluble carbohydrate administered by mouth is effective usually and can be reinforced by intravenous glucose if necessary. Until some starchy food is obtainable, soluble carbohydrate in small doses should be repeated each thirty

minutes. Bread and honey or bread and corn syrup form an effective antidote both for the immediate relief of the patient and for his protection against a subsequent attack when more insulin has been absorbed into the blood stream from the site of injection.

Unless precipitated by gross overdosage, fasting, indigestion, diarrhea or unusual and excessive exercise, reactions due to protamine zinc insulin administered in the morning will occur after six o'clock in the evening. With protamine zinc insulin, a reaction due to exercise may be delayed for many hours. Therefore, marked variations in the routine of living from one day to another should be avoided as much as possible to minimize this risk. When both insulins are being used in the morning, any reaction due to regular insulin will occur during the day and if a supplementary dose of regular insulin is used at supper time, a reaction due to it will occur before midnight. While not invariable, these rules indicate which insulin may require reduction. Not less than five units should be removed from a protamine insulin dose while two units reduction may suffice to abolish hypoglycemia from the regular insulin.

Local swelling due to the injection of protamine zinc insulin continues longer than that from unmodified insulin and may cause more prolonged discomfort. Sensitization reactions sometimes appear with increased local swelling: edema, urticaria, pruritus and even general symptoms may occur on rare occasions. In my own experience these have been usually of minor importance and were allayed by cold compresses or by allowing a saturated solution of magnesium sulphate to dry on the skin. Spontaneous desensitization usually will occur in two to three weeks if treatment is continued. More severe degrees of sensitization occur in patients who are already sensitive to the protein of the species from which the insulin is derived or in patients who have discontinued the use of insulin at some previous time. These are due usually to sensitization to the accompanying traces of species' protein but occasionally are due to insulin itself. When due to protein sensitization, another preparation of protamine zinc insulin may be tried or the patient may be given regular insulin derived from another species for a time, then gradually desensitized by substitution of small, but gradually increasing, doses of the offending insulin. Alternatively, crystallized insulin may be used and gradual desensitization carried out. If the patient is sensitive to insulin itself, he may be placed on an under-nutrition diet and desensitization carried out with crystallized insulin, either by the

Besredka or by the slow method, injecting the insulin in approximately the same spot repeatedly, as local desensitization precedes the general process.

Though antigenic properties of protamines have been denied, some cases of sensitization have been stated to occur. It is far from clear that they are not due to slight traces of accompanying fish protein rather than to the protamine itself. We have failed thus far to encounter this difficulty which doubtless could be surmounted by placing the patient on unmodified insulin temporarily and desensitizing with small doses of protamine zinc insulin or pure protamine solutions.

The greatest source of difficulty with protamine zinc insulin is impatience. This insulin is slow acting and cumulative and time is required for its full action to develop. Premature increase in the dose to hasten the action results in hypoglycemia, though on the same day the patient may have had glycosuria from the carbohydrate of the meals. Not less than four to seven days on a certain regimen is adequate to determine whether it is satisfactory, though it may be possible in shorter time to determine that a program is unsatisfactory. Hasty conclusions on this point should be avoided.

Finally, with adequate preliminary investigation and control, all diabetic patients requiring insulin will do better on protamine zinc insulin, or on a combination of protamine zinc insulin and regular insulin. No suggestion that a complete solution of the problems of the most severe and unstable cases of diabetes has been accomplished is warranted but we have been gratified to find that better control of such cases may be obtained by the use of protamine zinc insulin than was previously possible and many are markedly improved. For those with a lesser degree of severity, one may say there is an improvement in their general health, a reduction of the number of doses, economy of insulin, improvement of the twenty-four hour blood sugar level, and superior control of azoturia and ketonemia. There is also a diminution in the frequency of reactions though, when these do occur, they may be more difficult to diagnose and treat effectively. The patient has much greater freedom of action, and there are numerous indications that a slow but very definite improvement of tolerance occurs in some cases. Protamine zinc insulin has multiplied the problems of the physician treating the patient but for the latter, when he has been successfully stabilized, the outlook is improved immeasurably.

THE TREATMENT OF POSTABORTAL AND POSTPARTUM SEPSIS, WITH SPECIAL CONSIDERATION OF SULFANILAMIDE AND ALLIED DRUGS*

EDWARD G. WATERS

IN CONSIDERING new therapy for old diseases, we must not repeat an error of the eighteenth century, when the medical world forgot the teachings of White of Manchester, grudgingly to relearn them seventy years later from Semmelweis. There is much new to be learned and much old to be remembered in the treatment of postabortal and postpartum sepsis.

Postabortal sepsis usually follows induced, rarely spontaneous, abortions. There is generally the element of reinvasion of the uterine cavity without adequate asepsis, and usually there is retained detritus. Since the uterus is of smaller size than in the postpartum state, with less developed venous circulation, septic thrombophlebitis is less often seen than in puerperal sepsis, and subinvolution is not a common factor in causing postabortal bleeding. Traumatic invasion of the uterine wall or perforation make direct peritonitis a more common complication in postabortal infections. Therapy in postabortal sepsis more frequently demands gentle removal of infected, necrotic intrauterine debris, than in postpartum infections. Otherwise, these two conditions resulting from septic invasion of a uterus recently pregnant may be considered together from the standpoint of therapy.

Before detailing treatment, it is important first to consider some of the factors and agents which make it necessary. We have spoken of unclean intrauterine manipulation followed by reinvasion, with incomplete emptying of the uterine contents, as responsible for an overwhelming majority of postabortal septic cases. Here as in postpartum sepsis, we have bacterial transplant into a fertile field with open tissue spaces and vessels. In postpartum sepsis there is generally a history of long, exhausting labor with terminal traumatizing operative vaginal delivery,

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From the Margaret Hague Maternity Hospital, Jersey City, New Jersey.

associated with larger breaks in continuity of tissue than is commonly encountered with spontaneous vaginal delivery. But we must remember that even in normal cases, the uteroplacental site is a huge open wound, filled with soft blood clots occluding large sinuses, and the cervix is the site of multiple small abrasions and areas of superficial necrosis. Obviously, the groundwork for bacterial invasion is always present in the postpregnant genital tract.

Infective organisms must come from somewhere to produce infection and the sources are either endogenous, from the patient herself, or exogenous, introduced by another person, directly or indirectly. We cannot deny the possibility that the normal bacteria in the vagina suddenly change from innocuous to virulent forms when conditions are unusually favorable. But we do know that such change is unusual and that a bacterium generally maintains and seldom alters the inborn virulence of its own generation. A marked depression in the resistive factors of an individual might endow such an organism with a relative increase in virulence. This is true especially of the anaerobic nonhemolytic streptococcus. But it is my belief that most bacteria of high invasive properties are introduced shortly before, during or after the uterus is emptied. The high proportion of infected cases occurring in women who have had exhausting labors and traumatizing deliveries, pregnancy toxemias, chronic systemic disease, or excessive blood loss is significant. It suggests that invasion and diffusion, which characterize the degree of bacterial virulence, are also dependent upon lowered resistive factors.

An analysis of operative deliveries will show morbidity thrice that for normal cases if the membranes have been ruptured and/or the patient in labor more than twelve hours. Likewise, vaginal examinations introduce a danger that becomes serious when they are unclean or frequently done. Routine rectal examinations are far safer for the mother, and inherent hazards for the fetus are minimized by supplementing rectal with vaginal examinations when in doubt.

Certain changes in the maternal organism, such as increased blood volume, increased circulatory, metabolic and cellular activity, and increased phagocytosis, promote greater resistance to infection during pregnancy. Over and above this are the natural resistive factors to be found in all fixed and circulating tissues, and in the event of infection, acquired immunity developing in the host.

The types of organisms are numerous including various strains of streptococci: hemolytic, non-hemolytic, aerobic and anaerobic; various staphylococci; colon bacillus, gonococcus and pneumococcus, as well as the gas-forming anaerobes. The streptococcus and staphylococcus account for about 95 per cent of all puerperal infection, and nine of ten cases assuming any serious degree of virulence are caused by streptococci. The gonococcus and colon bacillus rarely cause virulent sepsis; the latter is generally a parasite or saprophyte.

The pleomorphic character of the infecting agent, and the varying response of the host make the determination of the responsible organism almost indispensable to antibacterial therapy. But with streptococci and staphylococci accounting for nearly 95 per cent of all postabortal and postpartum sepsis, we may presume one of these to be the active agent when bacteriologically it is impossible to indict the responsible organism. This, as we shall see, is an important therapeutic premise.

Manner of Invasion

There are two routes by which invasion of the infecting organism progresses:

1. Through the vessels at the placental site. This is often seen in virulent postpartum streptococcic infections or with infected incomplete abortions. Then, too, extension of this infection with thrombosis of the veins in the broad ligaments is commonly seen with organisms of low virulence, generally emanating from infected veins in the subplacental area. Here most commonly noted are the anaerobic streptococci which pass on to low-grade pelvic thrombophlebitis. While there is much concerning thrombus formation which we do not know, one fact we do know is that the most important factor in the production of a thrombus is venous wall infection, whether it gets there by way of perivenous lymphatics or through the damaged endothelial lining. With infection at the uteroplacental site, the infecting organism reaches the lacerated vessels and initiates a process, the extent of which is determined by the character of the organism, the resistance of the host, and the rapidity with which the resistive forces can be mobilized. With a virulent organism and little resistance, the thrombosis may not extend beyond the uterine wall and the patient may succumb within a few days with no involvement of the larger veins. With marked resistance and lessened virulence, the process of thrombus formation may progressively in-

volve the vessels of the broad ligament, pelvis and the vena cava, and the duration of the infection may last for weeks. The frequent occurrence of emboli and infarction complicates the picture and alters the treatment.

2. Through the lymphatics. Infection by way of the lymphatics of the uterus and broad ligament, and reaching the general circulation through the thoracic duct, is another path of invasion. This route is not commonly followed but when occurring, is associated with a highly virulent form of general sepsis, with a paucity of pelvic symptoms and pathology. Peritonitis may occur subsequent to lymphatic invasion, through extension from the broad ligament or subserosal lymphatics to the peritoneum.

Prophylaxis

The lessening of the incidence of infection and death from abortions lies in respect for moral and medical ethics and in abolishing the performance of surgically unclean abortions. Where therapeutic abortion is indicated, proper hospital management and care will adequately solve the problem. Judicious distribution of adequate instruction in birth control should minimize the need for abortions.

Prophylaxis of puerperal infections can be summed up in two words —good obstetrics. We may subdivide those two words into their applicable component parts: 1) during pregnancy, 2) during labor, 3) during delivery and 4) in the postpartum state. Prenatally, it is necessary to appraise the general condition of every mother through complete physical examination with detection of any systemic disturbances or abnormalities. An adequate and proper pelvic examination will give an estimation of the pelvic capacity upon which a prognosis can be made before labor begins. Avoiding the development of toxemias is also imperative since they notably increase the incidence of puerperal sepsis. Proper dietary control with intake of vitamins A, C and D, especially in the last half of pregnancy, requires stressing. Oral cleanliness and routine gargling is advocated for all patients with a history of recurrent sore throat and upper respiratory infections. Common sense observation of the patient, in addition to the use of the stethoscope, the manometer, the test tube, and weight scale, afford protection to most expectant mothers.

During labor a few essentials must be observed. Any examination must be cleanly made, whether rectal or vaginal. Rectal examinations

in the presence of a vaginal discharge require care, since the posterior vaginal wall must be pressed against the cervix. No pregnant patient should be touched during labor by an attendant without thoroughly scrubbed hands. A mask, preferably an impermeable type of mask, should be used during an examination. The vulva of the patient must be properly prepared and cleansed. There is considerable difference of opinion as to the value of vaginal antiseptics routinely used during labor. Reports as to their value are contradictory, yet it would seem good sense to use some worthwhile type of intravaginal antisepsis in all patients who present themselves in labor with a vaginal discharge. All personal contacts with patients in labor should be checked and recorded, and streptococcus carriers, especially those with infections in the upper respiratory passages, should be barred from labor and delivery rooms. All potentially or actually infected patients should be isolated and treated apart from the others in labor.

During Delivery. The infection rate is high in patients with long labors and ruptured membranes especially when complicated by traumatizing delivery. It is important to recognize early in the second stage the need for terminating labor by operation, if one would avoid an unduly high incidence of infection. Prolonged general anesthesia is to be condemned, for properly given spinal anesthesia, gas-oxygen, or local anesthesia with a patient well under analgesia, is far safer. During labor the patient should be protected against undue exposure and heat loss. Excessive loss of blood during delivery materially lessens resistance. The "12-hour safe period" should be observed for cesarean section cases. This means that the operator should decide, if able, within twelve hours of the onset of labor or within twelve hours of the rupture of the membranes as to whether or not a cesarean section need be done. The incidence of infection in this group under twelve hours is not higher than for vaginal deliveries. Where the membranes have long been ruptured and the patient long in labor, with or without fever, an extraperitoneal cesarean section should be seriously considered. It will protect from marked morbidity, and possible death, many patients in the potentially infected groups.

Postpartum. Excessive blood loss should be replaced by transfusion, with intravenous glucose to maintain blood volume and pressure until blood is available. Every bleeding and every toxemic case should be typed before delivery and a suitable donor held within call. Involution should

be hastened by the use of oxytocics. Prophylactic chemotherapy, of which I shall presently speak, should be used in presumably infected cases. All symptoms of shock should be overcome immediately. In applying the postpartum perineal pads one should avoid massaging bowel content into the vagina. Extreme care is needed when catheterizing the patient and giving enemas, especially when perineal incisions or lacerations exist. The perineal attendant should be masked, and if there are any upper respiratory infections, nothing but an impervious mask should be used. All infected cases should be isolated.

Treatment

Since the patient's recovery depends upon the outcome of a battle between the invading organism, with its virulence, volume and rapidity of spread unknown, and the patient's own resistive forces, obviously it is all important to assist in conserving her mental, moral and physical resources. She is kept happy in a light, airy room, free from noise and disturbance. An appetizing, high caloric diet supplements copious water and fruit-juice ingestion. High position in bed and frequent, gentle turnings combat hypostasis without involving too great danger from thrombotic emboli. A low enema daily evacuates the bowel, and distention is relieved by rectal tube and injections of prostigmin or pitressin. Relief of pain and avoidance of exhaustion call for pantopon or morphine, and denial of visitors. Diarrhea is checked with starch and opium enemas, and alcohol sponging with ice caps to the head symptomatically relieves the hyperpyretic crises. The only surgical treatment of postabortal infections consists in removing retained infected detritus from the uterus with sponge stick and forceps. Cul de sac abscess and pus accumulations pointing in the inguinal region, occasionally seen in postabortal or postpartum sepsis, require draining when pus is present in a recognizable amount. Unless the uterus must be emptied of its contents because of hemorrhage, it is usually best left alone. Douching is employed only to remove the fetid material and discharge which is commonly noted in anaerobic infections. Oxytocics and short wave therapy hasten involution. When in doubt the safest thing by far is nonmanipulation of the uterus.

It is necessary to actively combat the invading bacteria. There are ways in which this may be attempted, namely, vaccine therapy, serum therapy, non-specific therapy, blood transfusion and chemotherapy.

Vaccine therapy has been largely abandoned in the treatment of puerperal and postabortal sepsis, and there is no reputable record indicating that it is of value. The time element alone militates against its success. Active immunization is of doubtful theoretic worth. Too many patients would have to be immunized against too many possible infections to make it seem worth the effort.

Serum therapy is not new, having been introduced in France in 1895. Habitually it is being rediscovered and optimistically brought forward as a sure-cure, generally by that man who "once had a case." Such favorable reports as are available seem to indicate that the beneficial results obtained are through antitoxic rather than bactericidal action. Often the results are similar to those of non-specific protein therapy. It is quite possible that worthwhile sera may yet be produced. To date, we are still waiting.

Non-specific therapy is a stepchild of vaccine therapy, and is dependent upon the effects of a generalized systemic reaction induced by some agent, such as a split protein. It is very difficult to assess honestly the value of this form of treatment, but we think it may be of use in low-grade chronic infections associated with little systemic reaction. It induces a leukocytosis, fever, and promotes phagocytosis. In virulent infection, when there is evidence of marked systemic reaction, its value is very dubious. A good preparation is 5 to 10 cc. of fat-free boiled milk given intramuscularly daily.

Blood transfusions are invaluable in sepsis. Used adequately and early, they combat shock and blood loss and often prevent sepsis; and once sepsis appears, counteract the anemia which rapidly develops. In a sense transfused blood acts as a non-specific agent and stimulates the reticulo-endothelial system of the recipient to increased cellular antigenic resistance. In combating active infections, it is our practice to give transfusions of 150 to 250 cc. of blood at intervals of two to four days. These are either direct or citrate; if the latter, the blood may be taken from a blood bank or if from a single donor, a large amount may be taken and kept to be distributed over a period of days in small amounts.

In our opinion, specific immunotransfusions are of unusual value. We have seen enough favorable and occasionally startling responses to make us believe in their worth. Donors are so difficult to get and the bacterial strains so numerous, however, that this is a little used therapeutic procedure. When the hemoglobin and red cell volume is high, as

seen by blood count and hematocrit determinations, then the cell-free serum of the specific blood may be used, in 150 to 250 cc. amounts every other day. Otherwise, the whole blood is used.

Chemotherapy

Chemotherapy in sepsis is the attempt to sterilize the blood stream and infected tissues of the patient by an injected or an ingested chemical agent. In years past, almost everything has been tried, and the optimistic claims for perennial cures leaves us doubtful and cynical.

The latest agents to gain attention are the derivatives of sulfanilamide and sulfanilamide itself. The first article in English by Colebrook and Kenny focused attention on the possibilities of specific chemotherapy in puerperal infections. Using prontylin and prontosil, now known as neoprontosil, Colebrook reported results not attainable with other forms of therapy. Since then, experiments and analyses by Long and Bliss, Brown, Fuller, Coman, Bannick, Lockwood, Coburn and others, have improved our understanding of the action, dosage and dangers of sulfanilamide and its compounds. Since sulfanilamide and neoprontosil are the two drugs in most common use, we will confine our discussion to these.

Seemingly these two drugs exert the same therapeutic effect. In addition, neoprontosil may be given intramuscularly to patients who are unable to take the drug by mouth. Recent experience with another sulfanilamide derivative, sulfapyridine, would tend to verify the existing belief that the action of neoprontosil is due to its own molecular constitution, rather than the amount of sulfanilamide which its reduction in the body liberates. Gross, Cooper and Lewis have indicated that neoprontosil has the ability to inhibit the hemolysin of hemolytic streptococci, while Huntington demonstrated that sulfanilamide exerted no such inhibition. Both drugs seem to inhibit growth and damage the organisms affected, permitting marked phagocytosis by leukocytes and later monocytes. The work of Long and Bliss indicates that this is true. Colebrook and Kenny demonstrated inhibition of the growth of the organisms themselves if the drug is given sufficiently early. Apparently there is no chemotropic effect and according to Coman the drug does not attract leukocytes. These drugs act as chemotherapeutic agents combating not only the organism but its toxic effect, but do not kill off directly the infectious organisms themselves. Organisms subjected to their effects lose virulence, and their growth is inhibited. Lockwood and

his co-workers believe that the drug interferes with the faculty of virulent hemolytic streptococci to obtain nitrogen from the serum protein or necrotic substances. Thus, we may say that while the exact mechanism of its antibacterial activity is not clearly known, and while end results of toxicity are yet to be resolved, sulfanilamide and its derivatives possess specific chemotherapeutic action upon certain bacteria. Neoprontosil seems to be tolerated somewhat better than sulfanilamide and is less toxic. Like sulfanilamide, it is rapidly excreted, about 90 per cent being eliminated in the urine within five hours of its administration.

The toxic symptoms ascribed to sulfanilamide and its derivatives appear to be caused by a sensitivity to the drug and an idiosyncrasy toward it. The symptoms are generally mild and are referable to the gastrointestinal and central nervous systems. Nausea, anorexia, malaise, dizziness, tinnitus and mental confusion are among the earliest symptoms noted. Cyanosis occurs in 25 to 50 per cent of cases after sulfanilamide ingestion; is much less frequently noted with neoprontosil and is rarely of moment. It is due in part to methemoglobinemia and sulfhemoglobinemia. Curtailment or temporary suspension of drug dosage leads to complete cessation of the symptoms. A progression of the symptoms leads to cramps and diarrhea, paresthesias, fever, abdominal and precordial pains, maculopapular skin rash, progressive anemia, hepatitic or hemolytic jaundice, and granulocytopenia. These toxic symptoms are made worse by any existent renal or blood diseases or hepatic deficiencies. The blood count and blood smear must be watched and the drug discontinued if symptoms persist or recur, or if there is evidence of agranulocytosis. In our own experience, we had one case of agranulocytosis develop under sulfanilamide therapy with an eventually fatal outcome.

The organisms especially influenced are the hemolytic streptococci, gonococci, colon bacilli, and B. melitensis. Little effect seems to be noted in infections with Streptococcus viridans, hemolytic and non-hemolytic staphylococci, tubercle bacilli and pneumococci. The more recently developed sulfapyridine promises better results in some of these infections, notably against pneumococci.

Observation on the absorption and excretion of the drug indicates that an equilibrium can be established and a constant blood concentration maintained by repeating the drug dosage at four-hour intervals. A level of 5 to 10 milligrams per 100 cc. of blood is an optimum level for most infections. Long advocates a concentration of 10 milligrams per

100 cc. of blood attained early and maintained until definite clinical improvement has been obtained or until toxic symptoms force discontinuance of the drug. More recently he has advocated even higher concentrations although in our experience it is extremely difficult to attain them. In milder cases effects may be obtained by administering 60 to 90 grains a day distributed in six doses at four-hour intervals. Another means for calculating dose is by the body weight, giving 15 grains daily for every 20 pounds of body weight in four or six doses. Thus the dose for a person weighing 160 pounds would be 120 grains or 20 grains every four hours. The usual dose of neoprontosil ranges from 5 to 15 grains every four hours. Both drugs preferably are given with the stomach relatively empty to avoid discomfort and nausea. When the blood sulfanilamide level can be followed; give relatively heavy doses at first in order to obtain the desired blood concentration, and then diminish the dose to the point at which the attained level may be maintained. When parenteral use of the drug is indicated, 0.8 per cent solution of sulfanilamide in physiologic saline solution is given, or neoprontosil solution 5 to 10 cc. of a 2½ per cent solution intramuscularly every four hours. In calculating neoprontosil solution according to body weight, 1 cc. of a 2½ per cent solution is given for each pound body weight up to 120 pounds which represents the maximum daily dosage. Again, this is divided into four or six injections a day. Clinical improvement may be expected within forty-eight hours, and the dosage commonly diminished thereafter. In using sulfanilamide or neoprontosil it is essential to continue treatment well beyond the time when the blood culture is negative and the patient seems free of infection. Disregard of this admonition will result in frequent recurrence and relapse.

In a two-year period, representing 10,830 deliveries, we had 464 cases morbid with pelvic infection. The majority were mild cases of endometritis subsiding under a regime which consisted of postural drainage, short wave therapy, oxytocics, avoidance of internal or external manipulation involving the uterus, and maintenance of the patient's general systemic condition with frequent use of blood transfusion. There were some cases of localized parametritis which responded satisfactorily to short wave therapy of the pelvis, foreign protein injections, bowel hygiene, pain relief and sedation.

Fifty patients were treated with sulfanilamide and there were four deaths in this group. Eleven patients had repeated positive blood cul-

tures, nine of which were hemolytic streptococci and one non-hemolytic. Eight of these ten patients with streptococcic septicemia recovered, a result which was not paralleled in our previous experience when sulfanilamide or neoprontosil were not available. All other forms of supportive therapy were used exactly as heretofore, this time in conjunction with these drugs. One of the deaths ascribed to peritonitis following hemolytic streptococcic septicemia did not have adequate sulfanilamide therapy. The total dose was only 320 grains and the drug was then stopped because the blood count dropped to less than 3,000 white cells. Other therapy was continued including repeated small blood transfusions totalling 1500 cc. of blood over a period of ten days. The second patient to succumb with a hemolytic streptococcic septicemia was a 28-year old multipara admitted to the hospital in a desperate condition with postabortal sepsis after having had an abortion performed fourteen days earlier. The total amount given her was 125 grams (nearly 2,000 grains) of sulfanilamide given over a period of twenty days with a blood prontylin which ranged from four to as high as twenty, with the level being generally maintained at about 10 milligrams per 100 cc. She eventually died and at autopsy was found to have multiple lung abscesses. There was one patient with a positive B. coli septicemia who recovered. Of the thirty-nine patients whose blood cultures were either negative or not done, two died; one from an abruption of the placenta followed by cesarean section and peritonitis, and the second, from regional ileitis with postpartum intestinal obstruction, operation, and terminal peritonitis. The total sulfanilamide or prontylin dosage in the first case was 150 grains over ten days, and the second had neoprontosil solution 200 cc. over a period of seven days. Obviously both of these dosages were inadequate. Judging from our experience in these fifty cases, it would seem best to give a heavy initial dose to attain an early therapeutic effect, give it early in the course of the disease, and maintain it, to avoid recurrence, until the patient gives clinicopathologic evidence of resistance or cure of the infection and is also symptomatically well. We have not before experienced such success in handling postabortal and postpartum sepsis associated with blood stream infections as has been our lot since using sulfanilamide and neoprontosil.

Treatment of Pyelitis in Pregnancy

We have records of only sixteen cases of pyelitis of pregnancy

treated with sulfanilamide or neoprontosil. To evaluate it as a urinary antiseptic, it is necessary to determine whether the pyuria is an evidence of pyelocystitis or whether there is a coexisting pyelonephritis. The physiologic dilatation of the ureter with sluggish or absent peristalsis and atony, resulting in urinary stasis, makes pyelitis a common complication of pregnancy and one which is often treated with difficulty. Until recently our procedure has been to handle these cases conservatively with the standard urinary antiseptics unless the patient had a temperature and gastrointestinal symptoms, or seemed to have systemic disturbance as a result of infection. About six years ago we instituted ureteral catheter drainage for prolonged periods of two to seven days, with renal pelvic lavage. This treatment, combined with free use of transfusions to combat co-existing anemia, seemed to relieve most of our severe cases. With bacteriologic determination of the causative agent, urotropin seems sufficient for many cases of colon bacillus infections, although sulfanilamide is the best urinary antiseptic that we have encountered yet for other forms of organisms except Streptococcus fecalis.

With this last named organism, mandelic acid or ammonium mandelate seems to be most useful. A dosage of 45 to 60 grains of sulfanilamide a day is usually sufficient and will give a blood concentration of 3 to 4 milligrams per 100 cc. of blood, according to Long and Bliss. This dosage of 10 grains every four hours is carried out day and night. Barr reports a series of sixty-four cases with cures of mild and severe forms of pyelitis in four to fourteen days using much smaller dosages. It is too early for us to evaluate our experiences with sulfanilamide and neoprontosil in pyelitis, although we may say at this time that we are favorably impressed with our results to date.

PATHOGENESIS AND PRESENT DAY TREATMENT OF URINARY INFECTIONS*

MEREDITH F. CAMPBELL

INFECTION of the urinary tract is one of the commonest diseases of man; its recognition and successful therapy is a matter of everyday clinical concern. Etiology and pathogenesis must be appreciated if rational therapy is to be instituted. Only the high points of the clinical and therapeutic problem will be considered; theoretic considerations and controversial phases must necessarily be eliminated from the present discussion. In the treatment of these infections, the medication employed is often of secondary importance; rather it is essential that the accessory etiologic factors, which are predominantly obstructive, be recognized and adequately treated. Failure to recognize the existence and nature of these accessory factors accounts for most therapeutic failures. The introduction of mandelic acid, sulphanilamide and, in persistent staphylococcal infection, neoarsphenamine has effectively relegated the formerly employed antiseptics such as methenamine, pyridium, acriflavine, caprokol, and methylene blue.

ETIOLOGY: The bacterial invaders are conveniently classified according to their Gram-stain reaction. The Gram negative organisms are predominantly bacillary and of the colon-typhoid group. Of these, the B. coli escherichia is the commonest invading organism yet B. lactis aerogenes is of only slightly lesser incidence. Therapeutically it is extremely important to know which organism is present since B. lactis aerogenes is far more chemoresistant than B. coli escherichia. Gonococcal infections of the upper urinary tract are too rare to merit discussion here. The ammoniogenic proteus bacillus is encountered in 8 to 10 per cent of persistent urinary infections.

Of urinary tract invaders, the Gram positive staphylococci are outnumbered only by Gram negative colon bacilli and bacteriologic studies made during the initial stages of acute urinary infection have sometimes

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indicated an even higher incidence of staphylococci than colon bacilli. In urinary infection the albus and aureus varieties of staphylococcus are of equal importance and pathogenicity. Streptococci are found in about a third of all cases of mixed urinary infection. The beta hemolytic variety is usually readily susceptible to sulphanilamide therapy.

The accessory etiologic factors in urinary infection merit scarcely less attention than the bacterial invaders themselves. Lesions which cause urinary stasis or urinary constipation are of greatest importance. It should be distinctly understood, however, that urinary infection may occur, and commonly does, in the absence of urinary obstruction. Yet here the infection usually disappears readily and is most unlikely to become a serious therapeutic problem.

Obstructive lesions in adults are generally acquired, but in children are usually associated with congenital malformation. The obstruction may be transient, as observed during pregnancy, at which time uterine compression of the ureters as they cross the bony pelvis produces urinary back pressure with dilatation of the upper urinary tract. Here the introduction of bacteria or the revivification of existent organisms is commonly followed by clinically important urinary infection. Therapeutically, recognition of the improper urinary drainage and its correction by the inlying ureteral catheter, may usually be relied upon to bring these patients through normal and satisfactory delivery. In an eight weeks old girl I examined because of persistent acute "pyelitis," urologic investigation disclosed an infected hydronephrosis secondary to congenital right ureteropelvic junction stricture. Passage of the catheter coincident to urologic examination restored urinary drainage sufficient to cause the temperature to drop to normal in 24 hours. These citations illustrate the importance of considering and treating the associated etiologic lesions in urinary infections of all varieties.

Routes of invasion: In discussing infections of the urinary tract the infection is assumed to be predominantly renal. Yet we know that sometimes the urinary infection which is commonly, loosely and inadequately designated pyelitis, is confined to the lower urinary tract. Here the infection doubtless enters through the urethra. On the other hand, the "cystitis" myth should be laid. Cystitis as an independent lesion is practically unknown; in most cases thus diagnosed because of urinary disturbances, the vesical inflammation is secondary to renal infection, known or unrecognized, or to posterior urethral or prostatic

inflammation with or without infection. When "cystitis" exists, consider it secondary to renal infection until proved otherwise.

In most urinary tract infections the invading bacteria reach the kidney through the blood stream or by lymphohematogenous invasion from a primary focus elsewhere. In direct hematogenous infection the organisms are usually derived from an enteric, cutaneous, respiratory, or dental focus, yet the bacteria may be present as etiologic factors in a specific systemic disease such as typhoid. In lymphohematogenous invasions of the kidney, the primary focus is frequently in such pelvic organs as the Fallopian tubes, seminal vesicles, or prostate. The bacteria are absorbed by and transported through the lymphatics, reaching first the lower regional pelvic lymph nodes and passing thence into the thoracic duct and general circulation.

PATHOLOGY: Convincing experimental evidence indicates that the kidney is not a bacterial filter; bacteria cannot pass the epithelial barrier of the renal collecting system without producing tissue injury even though the injury cannot be later histologically demonstrated. This point is of vast importance in the consideration of renal bacteriuria, the demonstration of which must be accepted as indicative of bacterial kidney injury, predominantly of the cortex.

The terminology of urinary infection merits brief consideration. As previously indicated the term pyelitis has been loosely applied to all varieties of urinary tract infection. In the usual renal infection the pathologic picture is that of an interstitial suppurative pyelonephritis in which the parenchymal lesion is of grave importance while the pelvic lesion is generally negligible. Yet there are several pathologic conditions which may clinically simulate so-called acute pyelitis or acute pyelonephritis. The more important of these conditions are:

Bacteriuria: In this condition the urine is usually hazy or opalescent with bacteria and if bacillary organisms predominate, the condition is designated as a bacilluria. Pus cells are few in number and often are entirely absent. In bacteriuria, the infection is commonly confined to the lower urinary tract yet the likelihood of upper urinary tract involvement cannot be disregarded. In bacteriuria, the institution of free urinary drainage, and the liberal administration of the newer antiseptics will usually sterilize the urinary tract.

Pyelitis: Renal infection limited to the pelvis has not been satisfactorily demonstrated in the human being. It has been observed during

the first few hours of experimental renal infection, especially of the ascending variety. Yet after two days it has been impossible to determine histologically whether the animal's renal infection was ascending or hematogenous. I strongly feel that until an adequate examination has been made, it is more proper to designate the condition as an acute or chronic urinary infection than to attempt a specific and pathologically undemonstrable diagnosis, such as pyelitis.

Pyelonephritis: This is the usual lesion in acute renal infection. Histologically it is characterized by myriads of interstitial suppurative processes, usually bilateral and universally distributed. Cortical involvement is generally more pronounced than medullary. The bacterial invasion is customarily through the blood vessels, but may be through the lymphatics. In either event the interstitial leukocytic infiltration and suppurative process are characteristically perivascular. Mild lesions may heal with neither clinical manifestations nor scarring. In advanced suppurative nephritis productive of symptoms, a variable reparative renal scarring must be expected. During the evolution of the suppurative process, there is cloudy swelling of the adjacent renal tubules and in serial section polymorphonuclear leukocytes can be demonstrated extruding their way from the interstitial lesion and between the swollen tubular epithelial cells into the lumen of the collecting tubules. Thus it is that most of the pus demonstrated in the urine of patients with renal infection originates in the interstitial suppurative process in the parenchyma rather than in the kidney pelvis or lower urinary tract.

As a therapeutic corollary excretory antisepsis can be effective only as the drug hematogenously reaches the suppurative focal infections in the kidneys. Chemotherapy may fail when the renal function is greatly depressed and the concentration of the drug excreted is bacteriostatically ineffective. Moreover, when urinary stasis exists, the congested, inflamed renal parenchyma involved by the urinary stagnation or back pressure is less able than normal to cope with the existent infection. Yet with the institution of free drainage, rehabilitation of the local renal defensive mechanism, and excretory antisepsis the bacterial invasion is usually readily controlled and often cured.

Infected hydronephrosis: The obstruction which causes the hydronephrosis is usually at the outlet of the renal pelvis but may be at any distal point. The renal changes are those of hydronephrotic back pressure injury plus the suppurative lesions described under pyelonephritis.

Yet the establishment of free drainage reinforced by chemotherapy will frequently overcome the renal infection. Sometimes the urinary obstruction in infected hydronephrosis can be eliminated only by surgical plastic procedure but in advanced disease nephrectomy may be required.

Pyonephrosis: This may be the end stage of an infected hydronephrosis in which generalized suppurative destruction of the kidney occurs or it may be a massive suppurative renal destruction without demonstrable obstruction. In any event, the kidney is functionally dead, an active toxigenic focus, and must be treated by removal rather than by chemotherapy.

Surgical treatment, usually nephrectomy, is life saving in certain acute massive hematogenous suppurative renal lesions such as the pyemic kidney; in the localized hematogenous suppurative lesion commonly designated as renal carbuncle; and in perirenal abscess which is predominantly hematogenous and staphylococcal in origin.

Symptoms: The clinical picture of acute urinary infection is well known and the diagnosis is usually correctly made, even though the accessory factors may be inadequately comprehended. In acute urinary infection the general symptoms are most prominent; a third to a half of adults will suffer no symptoms pointing to the urinary tract. The onset is usually abrupt with chills, fever, malaise and gastrointestinal disturbances; in the initial stages and lacking symptoms referable to the urinary tract, the usual diagnosis is grippe. In most urinary infections the manifestations of the acute stage disappear in seven or ten days yet the urine usually continues to show pus for a month or longer. Gastrointestinal disturbances will be outstanding in approximately half of patients with chronic urinary infection. With advanced renal injury neurologic manifestations – irritability, lethargy, forgetfulness, and stuporousness – may appear. Persistence of renal infection, acute or chronic, means increased pathologic severity and must definitely influence treatment.

No patient should be discharged as cured until at least two negative cultures of a catheterized specimen have been obtained.

Diagnosis: The history of sudden onset, chills, gastrointestinal and vesical disturbances, perhaps with pain in the renal region, at once suggests acute urinary infection. The diagnosis is confirmed by urinalysis in which we are particularly interested in the pus, blood and

bacterial content of the urine. Pus casts at once indicate pyelonephritis. In some instances pyuria and urinary infection are accidental findings in urinalysis coincident with physical examination or examination for some other condition. This is particularly true in children.

In the study of urinary infection, the method of specimen collection is paramount and in the female only specimens collected by catheterization are worth examining. External scrubbing of the introitus and external urethral meatus as a substitute for catheterization causes far more trauma than urethral catheterization and is bacteriologically inadequate. In the male, a satisfactory specimen for culture can be obtained if, after wide retraction of the prepuce, the glans and meatus are well sponged with an antiseptic solution, such as bichloride or oxycyanide of mercury 1:500, after which the patient passes a small amount of urine before voiding into a sterile receptacle. Unless the specimen can be collected in this manner from the male, catheterization must be employed. I have several times examined female patients referred for urological examination because of so-called chronic pyelitis and in whom the laboratory had always reported a grave pyuria which was subsequently determined to be of vulvar origin; catheterized specimens, previously not taken from these patients, were normal and sterile. I have also had a similar experience in young males with a tight prepuce in whom subpreputial debris collected in the voided urine had been misinterpreted in terms of renal infection. Circumcision was curative.

It must be recognized that failure to demonstrate pus does not rule out grave renal infection. This is best illustrated in renal carbuncle and perirenal abscess. Here the renal suppuration does not drain into the collecting tubules to appear as pus in the bladder urine, yet culture of this urine will regularly disclose the invading organism. These conditions and pure bacteriuria are perhaps the best examples of apyuric urinary infection.

When the acute urinary infection remains acute for longer than five to six days despite intensive therapy a urologic examination is indicated. In such cases obstruction or suppuration requiring instrumental drainage or surgical incision will usually be found. In some instances, the temperature following acute urinary infection does not come down to normal but remains at 99° or 99.2° F. Urinalysis will demonstrate that urinary infection persists. Failure to cure these patients by intensive medical treatment over a period of three to four weeks demands a

comprehensive urologic examination at which time the accessory etiologic factors will be demonstrated. Yet in chronic urinary infection successfully eradicated by the newer chemotherapy, the previous persistence of the infection strongly suggests that urinary stasis exists and these patients are entitled to an excretory urographic investigation before being discharged. In a surprising number, unsuspected obstructive uropathy will be demonstrated.

Prognosis: The importance of urinary infection in the young may be deduced from the death incidence of a fifth to a third in infancy and approximately 3 per cent in older children. In infants failing nutrition doubtless accounts for more deaths than bacterial toxemia *per se*. This indicates the therapeutic importance of maintaining nutrition in young patients with urinary infection. Adults rarely die from uncomplicated acute pyelonephritis but complicating or secondary pyonephrosis, perinephritic abscess, renal carbuncle, or pneumonia, for example, may be fatal. In short, the prognosis in urinary infection depends upon the severity of renal injury, the accessory etiological factors, extraurinary complications and the treatment.

Treatment: In the therapeutic management of urinary infection, we disagree with those who rush at once for the medicine bottle. These patients merit sickroom quiet and rest in bed until the temperature has been normal for forty-eight hours. Renewed fever on getting up calls for further bed rest.

There is no special diet. Easily digestible foods may be given; as the patient improves, the appetite will return. Only in infants is the maintenance of nutrition likely to be of vital importance. During the acute stage of the infection a high fluid intake is essential to promote diuresis and combat dehydration; an approximate intake of one ounce of fluid per pound of body weight is desirable. This may be given by mouth, hypodermoclysis or intravenous infusion; the addition of glucose in 5 to 10 per cent volume concentration helps to combat acidosis, the clinical manifestations of which so commonly predominate in the general symptomatology of acute urinary infection, especially in children. For the same reason the administration of an alkali such as sodium bicarbonate is rational.

It is usually extremely difficult to identify the primary bacterial focus of infection in urinary infection hence the therapeutic eradication of the focus is rarely accomplished.

In the detoxication of the patient intestinal evacuation will be more effective than any other single measure. In carrying this out mild catharsis with a saline compound or castor oil is reinforced by colonic irrigations given once or twice daily during the acute stage of the infection and at longer intervals as the infection subsides. The volume of tap water used for the colonic is more important than the fecal return; for a colonic irrigation in an adult we advocate the use of at least eight gallons of water. A competent nurse should be able to administer this much fluid without seriously disturbing the patient. The first day or two the return from the irrigation may be clear or contain only strings of mucus and relatively small amounts of fecal debris, but about the third or fourth day an amazing amount of feces will be recovered and coincident with this increased evacuation, the patient will show pronounced improvement.

CHEMOTHERAPY: In recent years the chemotherapy of urinary infection has undergone revolutionary changes. Many methods and drugs formerly extensively employed have been largely discarded. Alkalinization of the urine by the administration of sodium bicarbonate is effective only to the extent that the medication combats acidosis; the urinalysis indicates no improvement. Therapeutic urinary acidification *per se* is seldom successful but is invaluable in combination with methenamine or mandelic acid ingestion. The empiric changing of the urine reaction from acid to alkaline and vice versa is valueless. Caprokol, pyridium, methenamine, methylene blue and other so-called urinary antiseptics which formerly enjoyed wide use, during the past three years have been largely replaced by mandelic acid and sulphanilamide, and in the present discussion of chemotherapy only the last two drugs and neoarsphenamine will be considered.

The choice of urinary antiseptic will be guided by the bacterial invader, the renal function of the patient, and his drug tolerance. As a rule, the renal function permitting, mandelic acid is my first choice in the treatment of urinary infections, chiefly because of lesser toxicity than sulphanilamide. Yet we have no quarrel with those who prefer sulphanilamide when bacteriologically indicated. We employ neoarsphenamine for staphylococcal infections which respond neither to mandelic acid nor to sulphanilamide.

MANDELIC ACID: This chemical is bactericidal against most of the common urinary tract bacterial invaders when the urinary pH is 5.5

TABLE

SULPHANILAMIDE AND MANDELIC ACID THERAPY FOR URINARY INFECTIONS

SULPHANILAMIDE			*MANDELIC ACID* (ammonium or calcium salt)		
DOSE (IN 24 HOURS)					
	Grains	*Grams*		*Grains*	*Grams*
Under 2 years	5-10	.3 - .6	Under 2 years	30- 60	2- 4
2- 4 years	10-20	.6 -1.2	2- 4 years	60- 90	4- 6
5- 8 years	15-25	.9 -1.5	5- 8 years	75-120	5- 8
9-12 years	20-25	1.2 -1.5	9-12 years	120-180	8-12
Adults	25-80	1.5 -4.8	Adults	180-225	12-15
Average dose (Per 10 Pounds Body Weight)	5	0.3		18.75	1.25
BACTERIOLOGIC INDICATIONS					
Gram negative bacilli (B. coli escherichia, B. lactis aerogenes, B. typhosus)			Gram negative bacilli (B. coli escherichia, B. lactis aerogenes, B. typhosus)		
Staphylococcus			Staphylococcus		
Streptococcus hemolyticus			Streptococcus, hemolytic and non-hemolytic		
Proteus			Enterococcus (Streptococcus fecalis)		
Pyocyaneus (pseudomonas)			Pyocyaneus (pseudomonas)		
INEFFECTIVE AGAINST					
Enterococcus (Streptococcus fecalis)			Proteus (unless urine highly acid)		
FLUID INTAKE					
Restrict to 1200 cc. in 24 hours in adults Restrict only with great caution in children					
URINE REACTION*					
Preferably alkaline; coadminister sodium bicarbonate, or potassium citrate q.s.			Must be more acid than pH 5.5 Mandelic acid concentration greater than 0.5 per cent Give Ammonium chloride Ammonium nitrate Dilute hydrochloric acid q.s.		

* Best estimated by potentiometer or nitrazene solution or paper.

or less and the concentration of the mandelic acid in the urine is 0.5 per cent or greater. The bactericidal action is usually regularly satisfactory when the pH is 5.2 and the acid concentration 0.8 per cent or greater.

Mandelic acid excreted in the urine may produce renal irritation and for this reason is contraindicated when noteworthy renal disease or injury exists. This irritation may be manifested by desquamation of renal epithelial cells, by hematuria and the passage of casts. Moreover, in cases of important renal disease, the damaged kidney frequently fails to excrete mandelic acid in amounts sufficient to be bactericidal. Thus the therapeutic course is not only unsuccessful, but mandelic acid may accumulate to a dangerous degree (acidosis) in the body. For these reasons, the approximate renal function should be known before administration of mandelic acid is begun. In cases of serious renal injury sulphanilamide should be chosen rather than mandelic acid, bearing in mind that inadequate excretion of the sulphanilamide may also render its use ineffective and its cumulative retention in the body may become a serious toxic factor.

Mandelic acid salts are marketed chiefly in the ammonium variety as tablet, elixir, or syrup, yet I prefer the calcium mandelate tablet, especially since I have found it more easily administered to young children and with less disturbance than other mandelic acid preparations. The basis of drug computation I usually follow is that of approximately 2 grains of the salt per pound of body weight in 24 hours. In most instances the mandelic acid salt will sufficiently acidify the urine but should the pH not be below 5.5 after 48 hours of mandelic acid administration, an acidulating salt such as ammonium chloride, calcium chloride, ammonium nitrate, or dilute hydrochloric acid should be administered at the same time in sufficient quantity to bring about the desired urinary acidity. The urinary pH may be estimated approximately by the use of nitrazene test papers which are checked against a standard colorimetric scale. Because adequate urinary acidulation must be absolute for the successful employment of mandelic acid therapy, the titre of the urine should be estimated once and preferably twice daily during the therapeutic period.

The mandelic acid compound is administered for a period of eight to ten days; meanwhile periodic reexaminations of the urine are made. In successful cases the urine is often pus free by the fourth or fifth day.

Yet one should not rely on cultures made while the patient is taking the urinary antiseptic, since its bacteriostatic activity in the collected specimen may be sufficient to inhibit growth and render the culture sterile. However, if the therapeutic progress is favorable, we wait three to four days after stopping the medication and take an aseptically collected specimen for culture. If no growth is obtained in 72 hours, a similar specimen is subsequently taken and if two negative reports are obtained, the patient is discharged as cured to return in one month for a final bacteriologic check up. If this test of cure is regularly followed, the incidence of so-called "recurrences of pyelitis" will be vastly diminished. Most alleged recurrences are simply exacerbations of smoldering, unrecognized infections persisting after the clinical disappearance of an infection previously acute. These exacerbations usually follow the onset of acute focal infection elsewhere, such as rhinitis, bronchitis or enteritis.

If the intensive administration of mandelic acid for eight to ten days is unsuccessful and if bacteriologic indications permit, it is my practice to switch the patient to sulphanilamide therapy for a similar period.

SULPHANILAMIDE: Sulphanilamide is effective against the common Gram negative invaders of the urinary tract including the proteus bacillus, and also against most of the Gram positive cocci. Yet it is ineffective against the enterococcus (S. fecalis), an organism we have found in about 3 per cent of urinary infections in children.

The average dose of sulphanilamide is about 5 grains for 10 pounds of body weight, yet in young children I have frequently used doses disproportionately larger. Sulphanilamide acts best in an alkaline medium; sodium bicarbonate or other alkalinizing agent is administered between meals (so as not to interfere with digestion) in doses adequate to render the urine strongly alkaline. Because of this superior activity in an alkaline urine, sulphanilamide is usually readily effective against the proteus bacillus which by its ammoniogenic activity regularly produces extremely alkaline urine.

I do not believe we are justified in persisting with intensive administration of sulphanilamide for longer than eight to ten days at a time, although I am aware that many clinicians not only give larger doses than have been indicated here, but for much longer consecutive periods. My respect for the potential toxic properties of sulphanilamide is ever increasing. It is recognized that cyanosis in itself is of little clinical

importance. Yet one cannot always identify hematologic changes in time to prevent serious injury. I have recently experienced this in an adult who received only 25 grains (5 grain doses) of sulphanilamide during a 36 hour period. Yet during this time his previously normal blood count was reduced to 1,800,000 red cells per cmm., the leukocytes to less than 2,000 per cmm., the hemoglobin to less than 40 per cent; an acute hemolytic crisis occurred, and after three transfusions totaling nearly 2,000 cc. of blood, the patient's blood count was still 25 per cent below normal.

Apparently there is little difference in therapeutic activity of sulphanilamide and di-sulphanilamide in the urinary tract. During the past two months we have been studying the therapeutic effect of sulfapyridine in urinary infections in children but as yet can offer no conclusions.

NEOARSPHENAMINE: It has become more generally appreciated of late that staphylococcal infections of the urinary tract often will readily respond to the intravenous injection of neoarsphenamine when given in the same manner as in the treatment of syphilis. Urinary sterilization will commonly be accomplished with four injections and if six injections are fruitless, more should not be given. I have employed intravenous neoarsphenamine only as a last resort in the treatment of staphylococcal infections, largely because of the objections raised by intelligent patients who are keenly aware of its usual antiluetic application. In fact, in my experience its employment in the treatment of urinary infections in private practice requires considerable explanation to the patient.

If the acute urinary infection does not show definite response to intensive medical therapy as above outlined within one week, a urological investigation is indicated, as it is in chronic urinary infection not responding to intensive medical treatment for one month. Such urologic investigation nearly always will demonstrate some form of urinary obstruction as the principal accessory agent. It must be remembered that neuromuscular disturbances of the urinary tract – commonly designated as cord bladder – produce urinary stasis by engendering expulsive inertia with consequent stagnation. This condition invites urinary infection and perpetuates infection already established.

RESULTS: Two-thirds of non-tuberculous urinary infections can be eradicated by medicinal means. In the remaining third additional treatment will be employed according to etiologic indications. This may

mean, for example, conservative instrumental dilatation of a urethral or ureteral stricture, or the radical removal of a stone from a kidney, or perhaps nephrectomy. Thus in the diagnostic investigation of chronic urinary infection in children we have demonstrated practically every urologic lesion known to exist in the adult.

RENAL TUBERCULOSIS: It is notable that chronic caseous tuberculosis exists in about one in sixty cases of persistent pyuria in children, and in adults its incidence is even greater. The treatment of unilateral renal tuberculosis is surgical, yet the demonstration of tubercle bacilli apparently passed from a kidney which shows a normal pyelogram does not call for nephrectomy. Nephrectomy should be reserved for those organs in which a tuberculous process is urographically demonstrable. Bilateral renal tuberculosis is a sanatorium medical problem offering a hopeless prognosis.

SUMMARY: The clinical phases of urinary infection have been briefly discussed. The etiology and pathogenesis are of utmost importance in the rational selection of treatment. If one relies on medical therapy alone, his results will be far less satisfactory than those of the clinician who thinks first in terms of potential accessory etiologic factors, and notably obstruction, and secondarily considers chemotherapy. The choice between mandelic acid and sulphanilamide should rest first upon specific bacteriologic indication and secondly upon renal function and tolerance of the patient for the drug. With intelligent chemotherapy, about two-thirds of the common urinary tract infections can be cured. In the remainder, instrumental or surgical treatment must be combined with medicinal therapy.

LIBRARY NOTES

*AN EXHIBITION OF BOOKS ON THE GROWTH OF OUR KNOWLEDGE OF BLOOD TRANSFUSION**

Prepared by

GERTRUDE L. ANNAN

In Charge of the Rare Book and History Rooms

Early References to Blood Transfusion

1. Ovid, 43 B.C.-18 A.D.
   Metamorphoses with an English translation by Frank Justus Miller.
   London, 1929, opened at vol. 1, pp. 366-367.
   Medea said. "Come, draw your swords, and let out his old blood that I may refill his empty veins with young blood again."
   Borrowed through the kindness of the New York Public Library.
2. [A modern account of what has been called the first operation of blood transfusion.]
   In: Villari, Pasquale. *Life and times of Girolamo Savonarola,* London, [1918], opened at p. 151.
   This account of the blood of three young boys being given to the aged Pope Innocent VIII, 1432-1492, claims that the blood was injected into the veins, but there seems to be no proof of this. Another version states that the blood was offered as a drink to the Pope who refused it.
   See Ogle, *Harveian oration,* London, 1881, note 20, p. 107.
3. Ficinus, Marsilius. 1433-1499.
   De triplici vita.
   Florence, 1489, opened at fo.d_3r.
   This Italian philosopher suggests the giving of healthy young blood from the veins of the arm to the aged by means of suction.
4. Pegel, Magnus. 1547-ca. 1615.
   Thesaurus rerum, selectarum, magnarum, dignarum, utilium . . .
   [Rostock], 1604, opened at p. 112.
   A reference to a "rare surgical operation," which has been thought to be that of blood transfusion, although the account is so vague that the precise nature of the operation cannot be determined. The author of this very rare work was a physician and mathematician.
   Borrowed through the courtesy of the Preussiche Staatsbibiliothek, Berlin, Germany.
5. Libavius, Andreas. ca. 1546-1616.
   Appendix necessaria syntagmatis arcanorum chymicorum . . .
   Frankfort, 1615, opened at p. 8.
   This seems to be the earliest account of blood being transfused directly from the arteries of one man into the arteries of another. The author was an eminent German chemist and physician.
   Borrowed through the courtesy of Princeton University Library.

* Prepared in connection with the Graduate Fortnight on "Diseases of the Blood and Blood-forming Organs" held at The New York Academy of Medicine, Oct. 24 to Nov. 4, 1938.

FRENCH CONTRIBUTIONS TO BLOOD TRANSFUSION IN THE SEVENTEENTH CENTURY

6. Denis, Jean Baptiste. d. 1704.
Lettre escrite à . . . [Habert] de Montmor . . . touchant une nouvelle maniere de guerir plusieurs maladies par la transfusion du sang.
[Paris, 1667], opened at pp. 12-13.
An account of the first transfusion of blood from animal to man, performed June 15th, 1667. Denis was involved for years in controversy on the subject of transfusion and its dangers.
Photostat copy from the Bibliothèque nationale.

7. Lamy, Guillaume. fl. 1672.
Lettre escrite à . . . [Jean Baptiste] Moreau contre les pretenduës utilités de la transfusion du sang . . .
[Paris, 1667].
A response to Denis's arguments for blood transfusion, dated July 8, 1667.
Photostat copy from the Bibliothèque nationale.

8. Petit, Pierre. 1617-1687.
De nova curandorum morborum ratione per transfusionem sanguinis . . .
Paris, 1667.
A tract against transfusion by the physician and Latin poet, July 11, 1667.
Photostat copy from the Bibliothèque nationale.

9. Gadrois, Claude. d. 1678.
Lettre escrite à . . . l'abbé Bourdelot . . . pour servir de réponse au Sr Lamy, & confirmer en mesme temps la transfusion du sang par de nouvelles expériences.
[Paris, 1667].
A reply to Lamy in behalf of blood transfusion written August 8th, 1667, by the young scholar who became director of the military hospital at Metz and died at the age of thirty-six.
Photostat copy from the Bibliothèque nationale.

10. Tardi, Claude. 1607-1670.
Traitté de l'ecoulement du sang d'un homme dans les venes d'un autre . . .
Paris, 1667.
The first account of the technique of direct transfusion of blood from one man to another. While Denis was transfusing the blood of animals into man, Tardi published this detailed account of his technique in direct transfusion. There is no proof, however, that he put his theories into practice.

11. de Gurye, Gaspard. fl. ca. 1668.
Lettre . . . à M. l'abbé Bourdelot . . . touchant la transfusion.
Paris, 1667.
In: *Le journal des sçavans de l'an M. DC.LXVIII.* Amsterdam, 1679, opened at p. 313.
A contemporary review of the work by Gurye which contains the "first warning of the dangers attending the administration of incompatible blood" (Keynes). An English account is found in *Philosophical Transactions . . . abridged . . .* London, 1809, vol. 1, p. 183. Gurye notes both the advantages and evils of blood transfusion.

12. De la Martinière, Pierre Martin. 1634-1676.
Les opuscles . . . contre les circulateurs & transfuseurs de sang . . .
Paris, [1668].
Another tract against transfusion, written by the surgeon and traveler, with royal privilege to print dated June 16, 1668.
Photostat copy from the Bibliothèque nationale.

13. de Basril, Louis. fl. ca. 1667.
Reflexions . . . sur les disputes qui se font à l'occasion de la transfusion.
[Paris, ca. 1668].
Transfusion is championed by a layman, an "advocat en Parlement," who criticizes Lamy and De la Martinière for their attacks upon it.
Photostat copy from the Bibliothèque nationale.

14. Sentence rendue au Chastelet par Monsieur le lieutenant criminel le 17 avril 1668.
In: Oré, P. C. *Études historiques . . . sur la transfusion du sang.* 2. ed. Paris, 1876, pp. 42-44.
This decrees that in the future blood

transfusion cannot be done upon man without the permission of a physician of the Paris faculty, which had heartily opposed transfusion. The sentence was brought about at the instigation of a widow of one of Denis's patients. The patient, insane, had been treated by transfusion and considerably helped, but later died. The widow was aroused to action by Denis's adversaries.

15. France. Arrêt du Parlement de Paris du 10 janvier, 1670.

In: Villaret, Maurice et Montier, François. "Les origines de l'injection thérapeutique intra-veneuse."

In: *Paris médical,* **1921, vol. 42,** (annexe), opened at p. 120.

This Arrêt which forbids all doctors to practice blood transfusion is apparently not now in existence. The authors of the article give here the extant references to it.

English Contributions to Blood Transfusion in the Seventeenth Century

16. Oldenburg, Henry. 1615?-1677.

An account of the method of conveying liquors immediately into the mass of the blood.

In: *Philosophical transactions of the Royal Society of London [for the year 1665] . . . abridged . . .* London, 1809, p. 45.

Oldenburg, secretary of the Royal Society and editor of its *Transactions,* reports the discovery of this new experiment by the well known architect, Christopher Wren, 1632-1723. The Italian physician, Folli, later claimed that Wren had learned it from him.

17. Lower, Richard. 1631-1691.

Tractatus de corde . . .

Amsterdam, 1669, opened at p. 181.

Description of his technique of blood transfusion by the English physiologist who was the first in that country to perform the transfusion of blood from one animal to another, in February, 1665.

18. Boyle, Robert. 1627-1691.

The method observed in transfusing the blood out of one animal into another.

In his: *Works . . .* London, 1772, vol. 3, pp. 149-151.

The great scientist's account of Lower's experiment appeared in the *Philosophical Transactions* for December 17, 1666.

19. Lower, Richard. 1631-1691, and King, Sir Edmund. 1629-1709.

Transfusion practised upon man.

In: *Philosophical transactions . . . abridged and dispos'd under general heads . . . by John Lowthrop . . .* London, 1705, vol. 3, p. 231.

Record of the first human transfusion in England on November 23, 1667. Sheep's blood was used. The *Philosophical Transactions* of the period contain accounts of the many experiments in England and elsewhere.

20. Pepys, Samuel. 1633-1703.

The diary . . . with Lord Braybrooke's notes edited . . . by Henry B. Wheatley.

London, 1895, vol. 6, opened at p. 67.

The famous diarist made several references to the transfusion experiments. In this one he mentions the opinion of the scientist, Robert Hooke, 1635-1703.

Contributions of Countries Other Than England and France in the Seventeenth Century

21. Folli, Francesco. 1624-1685.

Stadera medica nelle quale oltre la medicina infusoria . . . e le contrario alla trasfusion del sangue . . .

Florence, 1680, opened at p. 35.

This Italian physician claims that after reading Harvey's work on circulation in 1652 he saw the possibilities of transfusion and in 1654 conducted experiments before Ferdinand, Grand Duke of Tuscany. He claims further that the English scientists heard of his experiments, but gave him no credit for the discovery.

22. Major, John Daniel. 1634-1693.

Chirurgia infusoria . . .

Kiel, 1667, opened at p. 2.

A contemporary illustration depicting

the operation of the injection of medicines into the veins. On p. 212 of this work, the author describes blood transfusion.

Borrowed through the courtesy of the Army Medical Library.

23. Ettmüller, Michael. 1644-1683.
Dissertation sur l'infusion des liqueurs dans les vaisseaux.
In his: *Nouvelle chirurgie* . . . Lyons, 1691, opened at p. 511.
Published first in 1668, this contains a recommendation for the infusion of human blood in the veins in the treatment of fevers.

24. van Lamsweerde, Jan Baptist. fl. ca. 1700.
Appendix . . . ad Armamentarium chirurgicum . . .
In: Scultetus, Joannes. *Armamentarium chirurgicum* . . . Leyden, 1693.
This contemporary illustration of the technique and instruments used in blood transfusion appeared first with the 1672 edition of Scultetus.

25. Bartholinus, Caspar. (the younger) 1655-1738.
De chirurgia transfusoria.
In: Bartholinus, Thomas (the elder). *Acta medica et philosophica* . . . Copenhagen, 1677, vol. 3, p. 86.
A note on transfusion from Paris by the well known Danish physician. "Transfusion underwent in Denmark the same fortune as in France and Italy, meeting there likewise with its adversaries, who brought it into discredit." (Ullersperger).

26. Mercklin, Georg Abraham. 1644-1702.
Tractatio med. curiosa, de ortu & occasu transfusionis sanguinis . . .
Nuremberg, 1679.
One of the most violent attacks on blood transfusion by a prominent German physician, who includes here a history of the subject.

27. Nuck, Antonius. 1650-1692.
Operationes et experimenta chirurgica . . .
Leyden, 1733, opened at p. 166.
Originally published in 1692, this advises the use of blood transfusion in a number of diseases, and complains that the operation has been neglected for some years.

28. Purmann, Matthäus Gottfried. 1648-1721.
Chirurgia curiosa: or, the newest and most curious observations and operations in the whole art of chirurgery . . .
London, 1706, opened at p. 304.
A description of transfusion by the eminent military surgeon, published originally in 1694. Purmann regrets that the operation was not then in general use and cites a case of leprosy which he cured by transfusion.

Blood Transfusion in the Eighteenth Century

29. Heister, Lorenz. 1683-1758.
A general system of surgery . . .
London, 1743, opened at vol. 1, p. 305.
The great German surgeon of the eighteenth century describes the operations of transfusion and infusion which "are seldom practised by our modern surgeons, yet they were highly celebrated, and often performed, in the last century, from the year 1660-1680 . . ." This work appeared in 1719.

30. Rosa, Michele. 1731-1812.
Lettre estemporanea sopra alcune curiosità fisiologiche . . .
[Napoli?], 1782, opened at p. 80.
Rosa's successful experiments on animals in February, 1783, were the first to be presented to the medical profession in many years.

31. Harwood, (Sir) Busick. 1745?-1814.
[Account of his experiments in blood transfusion].
In: *Philosophical transactions of the Royal Society of London abridged* . . . London; 1809, p. 185, note. Photostat copy.
Harwood was the first to revive interest in blood transfusion in England by his successful experiments on dogs in 1785

32. Seybert, Adam. 1773-1825.
*An attempt to disprove the doctrine of

* Inaugural dissertation.

the putrefaction of the blood of living animals . . .

Philadelphia, 1793, opened at pp. 54-55.

A series of experiments of an American physician who injected putrid blood into the veins of animals, to determine its effect upon normal blood.

33. Darwin, Erasmus. 1731-1802.
Zoonomia; or, the laws of organic life. 2. ed. London, 1796, opened at vol. 2, p. 605.

The famous physician and botanist suggests the use of transfusion in fevers, and describes the operation.

Blood Transfusion in the Nineteenth Century

34. Scheel, Paul. 1773-1811.
Die Transfusion des Blutes . . .

Copenhagen, 1802, opened at p. xv.

This excellent history of transfusion was compiled at a time when that method of treatment was seldom used and infrequently mentioned. The careful bibliography has been of inestimable value to those interested in the early history of the subject.

35. Prévost, Jean Louis. 1790-1850, and Dumas, Jean Baptiste André. 1800-1884.
Physiologie animale. Examen du sang et de son actions [*sic*] dans les divers phénomènes de la vie.

In: *Bibliothèque universelle des sciences* . . . Geneva, 1821, vol. 17, opened at pp. 226-227.

Although these experimenters had some success in bringing back to life by blood transfusion a horse which had been bled to syncope, their conclusions were that the operation was dangerous and should not be performed. They mention that in their experiments they used defibrinated blood or caustic soda as an anticoagulant.

Borrowed through the kindness of Yale University Library.

36. Blundell, James. 1790-1877.
Researches physiological and pathological . . . with a view to the improvement of medical and surgical practice . . .

[London], 1825, opened at pl. 2, p. [143].

Blundell's work "may be taken to mark the real beginning of the clinical application of blood transfusion." (Keynes). The plate shows his "impellor", the instrument he used in transfusion, this work gives the records of his operations.

37. Dieffenbach, Johann Friedrich. 1790-1847.
Physiologische Untersuchungen über die Transfusion des Blutes.

In: *Magazin für die gesammte Heilkunde . . . herausgegeben von Dr. Johann Nep. Rust* . . . Berlin, 1830, vol. 30, p. [3].

The experiments of this eminent surgeon led him to the conclusion that the blood of the same kind of animal should be used in transfusion, and that the blood of animals should not be injected in human veins.

38. Bischoff, Theodor Ludwig Wilhelm. 1807-1882.
Beiträge zur lehre von dem Blute und der Transfusion desselben.

In: *Archiv für Anatomie, Physiologie . . . herausgegeben von Dr. Johannes Müller*, Berlin, 1835, p. 347.

An account of the author's experiments with the injection of defibrinated blood to prevent coagulation.

39. Routh, Charles Henry Felix. 1822-1909.
Remarks, statistical and general, on transfusion.

In: *Medical times*, 1849, vol. 20, p. 114.

The author records all the known cases of blood transfusion in an effort to show that "the operation is one of the safest major operations which may be practised in surgery." Case no. 48 is an account of an operation of his own on a patient with cholera.

40. Brown-Séquard, Charles Edward. 1817-1894.
Sur la persistance de la vie dans les membres atteints de la rigidité qu'on appelle cadavérique.

In: *Comptes rendus hebdomadaires des séances de l'Académie des sciences* . . . Paris, 1851, vol. 32, p. 855.

The first of a number of articles on the experiments of this eminent physiologist. In this account he demonstrates that after the injection of blood into the arteries, muscles which have been attacked by rigor mortis, recover their voluntary movements. From later experiments he concludes that blood from the arteries given to animals by transfusion has a beneficial effect, whereas blood from the veins does not.

41. Louisiana State Medical Society.
On the question of transfusion—being a report of a Committee. Read . . . March 16th, 1853. By N. B. Benedict.
In: *New Orleans medical and surgical journal,* 1853, vol. 10, opened at pp. 204-205.
Description of an apparatus contrived by this Committee for facility in blood transfusion. The report contains a history of the subject as well as an account of Blundell's experiments. Benedict, a physician of New Orleans, joined the Society in 1852 and acted as Corresponding Secretary.

42. Higginson, Alfred. 1808-1884.
A report of seven cases of transfusion by blood, with a description of the instrument invented by the author.
In: *Liverpool medico-chirurgical journal,* 1857, vol. 1, p. [102].
"An important modification was introduced into the technique of the operation in 1857, by Higginson, who applied the principle of a rubber syringe with ball-valves for transferring the blood from the receptacle into which it was drawn to the vein of the recipient" (Keynes).

43. Richardson, (Sir) Benjamin Ward. 1828-1896.
The cause of the coagulation of the blood: being the Astley Cooper prize essay for 1856 . . .
London, 1858, opened at p. 448.
An account of experiments in which ammonia was employed in transfusion to prevent coagulation.

44. Martin, Eduard Arnold. 1807-1875.
Ueber die Transfusion bei Blutungen Neuentbundener.
Berlin, 1859, opened at pp. 18-19.
These tables contain fifty-seven cases of hemorrhage at child-birth treated by blood transfusion in the years 1824-1857. Forty-five out of the fifty-seven operations were successful.

45. Blasius, Ernst. 1802-1875.
Statistik der Transfusion des Blutes.
In: *Monatsblatt f. medicinische Statistik,* (supp. to *Deutsche klinik)* 1863, vol. 15, opened at pp. 80-81.
Out of a total of 116 operations, in different countries, Blasius found that 56 had succeeded, 55 failed, and 5 were in doubt.

46. Panum, Peter Ludwig. 1820-1885.
Experimentelle Untersuchungen über die Transfusion, Transplantation oder Substitution des Blutes . . .
In: *Archiv für pathologische Anatomie und Physiologie . . . von Rudolf Virchow,* Berlin, 1863, opened at p. 244.
Panum lists the first experiments of transfusing defibrinated blood into human beings and gives an account of the earliest one, done in 1847, by Sören Eskildsen Larsen, b. 1802. Panum served as Dieffenbach's assistant at the Almindelig Hospital in Copenhagen, and is remembered for his work on the pathology of embolism. He favored the use of defibrinated blood in transfusion because it avoided the risk of embolism.

47. Kühne, Willy. 1837-1900.
Verfahren bei Vergiftigungen durch Kohlenoxyd.
In: *Centralblatt für die medicinischen Wissenschaften . . .* Berlin, 1864, vol. 2, p. 134.
Kühne suggests the use of blood transfusion in the treatment of carbon monoxide poisoning.

48. Aveling, James Hobson. 1828-1892.
On immediate transfusion.
In: *Transactions of the Obstetrical Society of London,* 1865, vol. 6, opened at p. 133.
A contemporary illustration of the direct transfusion of blood in England in the nineteenth century.

49. Hicks, John Braxton. 1825-1897.
On transfusion and new mode of management.
In: *British medical journal,* 1868, vol.

2, p. 151.

An account of the treatment of blood with phosphate of soda to retard coagulation during transfusion.

50. Hueter, Karl. 1838-1882. . .
Vorläufige Mittheilung betreffend die Transfusion von fieberfreiem Blut bei acuten, das Leben bedrohenden Wund- und Eiterfiebern.

In: *Centralblatt für die medicinischen Wissenschaften,* 1869, vol. 7, opened at p. 390.

Hueter credits von Gräfe with the introduction of arterial transfusion and goes on to describe his own method of injecting defibrinated blood from the vein of one to the artery of another. His success led him to conclude that it allowed the blood to reach the heart more slowly than other methods and prevented air embolisms. For a more detailed account of his experiments, see his article on the subject in *Archiv für klinische Chirurgie,* 1871, vol. 12, p. 1.

51. Hooker, Ransom Spaford. 1873—
and Satterlee, Henry Suydam. 1874—
A special method for the transfusion of blood with the use of paraffin and hirudin.

In: *Operative therapeusis, edited by A. B. Johnson,* 1916, vol. 1, opened at p. 339.

A description of the four general types of instruments for blood transfusion devised from about 1830 to 1880 with the names of those who invented them.

52. Gesellius, Franz. fl. 1873.
Die Transfusion des Blutes . . .

St. Petersburg & Leipzig, 1873, opened at p. 19.

An illustration of the apparatus invented by this Russian physician to take blood from a healthy man for purposes of transfusion. In spite of his invention, Gesellius deplores the use of defibrinated human blood because of the lack of voluntary blood donors. He advocates the use of lamb's blood.

53. Moncoq, D. fl. 1874.
Transfusion instantanée du sang . . .

Paris, 1874, opened at folding plate.

Illustrations of different types of instruments designed by the author for use in the transfusion of blood.

54. Hasse, Oscar. 1837-1898.
Die Lammblut-Transfusion beim Menschen.

St. Petersburg and Leipzig, 1874.

Another advocate of the use of lamb's blood reports favorably on the outcome of his cases.

55. Madge, Henry M fl. 1859-ca. 1890.
On transfusion of blood .

In: *British medical journal,* 1874, vol. 1, opened at p. 44.

A report by the chairman of a committee of the Obstetrical Society of London appointed "to collect evidence, and to test, as far as possible, the real claims of transfusion to the confidence of the profession." Madge reports favorably upon transfusion but suggests 13 points calling for further inquiry.

56. Ponfick, Emil. 1844-1913.
Experimentelle Beiträge zur Lehre von der Transfusion.

In: *Archiv f. path. anat.,* 1875, vol. 62, p. [273].

Ponfick's experiments bring him to the conclusion that the transfusion of blood between animals of a different kind are injurious. He notes that hematuria results from such a transfusion and suggests that hemoglobinuria is a more descriptive name.

57. Landois, Leonard. 1837-1902.
Die Transfusion des Blutes . . .

Leipzig, 1875, opened at p. 184.

This important work shows the author's careful study of the changes which take place in the blood when transfused from one kind of animal to another. He points out the dissolution of the red blood corpuscles and the releasing of the hemoglobin.

58. Thomas, Theodore Gaillard. 1831-1903.
The intra-venous injection of milk as a substitute for the transfusion of blood . . .

In: *New York medical journal,* 1878, vol. 27, opened at p. 465.

This New York physician gives an account of cases in which he injected milk into the veins, instead of blood. He

predicts a brilliant future for "intravenous lacteal injection."

59. Halsted, William Stewart. 1852-1922.
Refusion in the treatment of carbonic oxide poisoning.
In: *Annals of anatomy and surgery,* Brooklyn, N. Y., 1884, vol. 9, p. 7.
This eminent American surgeon advocates the use of centripetal arterial infusion in the treatment of carbon monoxide poisoning.

60. von Ziemssen, Hugo Wilhelm, 1829-1902.
Ueber subcutane Blutinjection und über eine neue Methode der intravenösen Transfusion.
In: *Verhandlungen des* (11) *Congresses für innere Medicin,* 1892, opened at pp. 168-169.
This eminent physician's first method was the injection of blood subcutaneously. His later method was the withdrawal of blood into a syringe in order to inject it into the vein of the patient. He advised the use of three syringes and as many assistants.

61. Murphy, John Benjamin. 1857-1916.
Resection of arteries and veins injured in continuity—end-to-end suture—experimental and clinical research.
In: *Medical record,* 1897, vol. 51, opened at pp. 74-75.
Illustrations of end-to-end suture of veins and arteries which proved a great stimulus to surgery of the blood vessels.

Blood Transfusion in the Twentieth Century

62. Shattock, Samuel George. 1852-1924.
Chromocyte clumping in acute pneumonia and certain other diseases, and the significance of the buffy coat in the shed blood.
In: *Journal of pathology and bacteriology,* 1900, vol. 6, opened at p. 306.
An account of his discovery that the serum of a horse agglutinates the corpuscles of a human being.

63. Landsteiner, Karl. 1868—
Ueber Agglutinationserscheinungen normalen menschlichen Blutes.
In *Wiener klinische Wochenschrift,* 1901, vol. 14, p. 1132.
The author's account of his experiments showing that human blood contains isoagglutinins, capable of agglutinating other human red blood corpuscles. He divides human blood in three groups. Shattock's work was done independently.

64. Decustello-Rechtwehr, Alfred. 1872—
& Sturli, Adriano.
Ueber die Isoagglutinine in Serum gesunder und kranker Menschen.
In: *Muenchener medicinische Wochenschrift,* 1902, vol. 49, opened at pp. 1092-1093.
An account of the experiments which showed the discovery of the fourth and rarest blood group.

65. Carrel, Alexis. 1873—
La technique opératoire des anastomoses vasculaires et la transplantation des viscères.
In: *Lyon medical,* 1902, vol. 98, opened at pp. 862-863.
The first of Carrel's papers on end-to-end anastomosis of blood-vessels, which revolutionized the surgery of the vascular system.

66. Janský, Jan.
Haematologické studie u psychotiků.
In: *Sborník klinický,* 1907, vol. 8, opened at p. 132.
A resumé of the first account of the classification of human blood into four groups.

67. Hektoen, Ludvig. 1863-
Isoagglutination of human corpuscles.
In: *Journal of infectious diseases,* 1907, vol. 4, p. 297.
An account of experiments which led the author to point out the dangers of homologous blood transfusion arising from the common occurrence of isoagglutinins in human serum. This danger "can be avoided by the selection of a donor whose corpuscles are not agglutinated by the serum of the recipient, and whose serum does not agglutinate the corpuscles of the latter; that is to say, donor and recipient should belong to the same group and preferably to Group I or II."

68. Crile, George Washington. 1864-
The technique of direct transfusion of blood.

In: *Annals of surgery*, 1907, vol. 46, p. 329.

A description of Crile's method of direct blood transfusion which eliminated many dangers and was "the first to render the operation of transfusion a comparatively popular one" (Keynes).

69. Lambert, Samuel Waldron. 1859-
Melæna neonatorum, with report of a case cured by transfusion.
Repr.: *Medical record*, 1908, vol. 73, p. [885].
An account of the cure of a case of melæna neonatorum by means of direct blood transfusion by end-to-end anastomosis, performed by Dr. Carrel.

70. Ottenberg, Reuben. 1882-
Transfusion and arterial anastomosis.
In: *Annals of surgery*, 1908, vol. 47, opened at p. 505.
The author's experiments led him to the conclusion that transfusion would be made more safe if it is determined before-hand whether hemolysis is likely to occur when any two given bloods are mixed.

71. Elsberg, Charles Albert. 1871-
A simple canula for the direct transfusion of blood.
In: *Journal of the American medical association*, vol. 52, 1909, opened at p. 888.
Description of a simplification of the Crile canula.

72. Hartwell, John Augustus. 1869-
A simple method of blood transfusion without canula.
In: *Journal of the American medical association*, 1909, vol. 52, p. 297.
An account of experiments in which the end of the artery is slipped directly into the end of the vein.

73. Brewer, George Emerson. 1861- & Leggett, Noel Bleecker.
Direct blood transfusion by means of paraffin coated glass tubes.
In: *Surgery, gynecology and obstetrics*, 1909, vol. 9, p. 293.
The authors propose a new method to facilitate direct blood transfusion.

74. Crile, George Washington. 1864-
Hemorrhage and transfusion . . .
N. Y. and London, 1909, opened at p. 292.
Illustration of the stages of end-to-end anastomosis of two blood vessels by the canula method.

75. Moss, William Lorenzo. 1876-
Studies on isoagglutinins and isohemolysins.
In: *Bulletin of the Johns Hopkins hospital*, 1910, vol. 21, opened at p. 66.
The Moss classification of the blood groups. This was done independently of Jansky's work, and the use of both systems of classification caused confusion and actual danger.

76. Curtis, Arthur Hale. 1881- & David, Vernon Cyrenius. 1882-
Transfusion of blood by a new method, allowing accurate measurement.
In: *Journal of the American medical association*, 1911, vol. 56, p. 35.
Description of transfusion with a syringe and a two-armed canula which has been coated with paraffin on the inside.

77. Kimpton, Arthur Ronald. 1881- & Brown, James Howard. 1884-
A new and simple method of transfusion.
Repr.: *Journal of the American medical association*, 1913, vol. 61, pp. 117-118.
An account of indirect transfusion by means of a paraffin coated vessel.

78. Lindeman, Edward. 1879-1919.
Simple syringe transfusion with special cannulas . . .
In: *American journal of diseases of children*, 1913, vol. 6, p. 28.
This revival of Ziemssen's method employs two sets of canulas, two tourniquets and twelve syringes. The account was read at The New York Academy of Medicine on April 10th, 1913.

79. Abel, John Jacob. 1857- ; Rountree, Leonard George. 1883- & Turner, Benjamin Bernard.
Plasma removal with return of corpuscles (plasmaphæresis).
In: *Journal of pharmacology and experimental therapeutics*, 1913-1914, vol. 5, opened at p. 628.
An early experiment using hirudin to prevent coagulation.

80. Hustin, Albert. 1882-

Principe d'une nouvelle méthode de transfusion muqueuse.

In: *Journal médical de Bruxelles,* 1914, vol. 19, opened at p. 437.

This Belgium physician advocated the use of sodium citrate as an anticoagulant. In one case he employed a citrate solution mixed with glucose.

81. Agote, Luis. 1868-
Nuevo procedimiento para la transfusión del sangre.

In: *Anales del Instituto modelo de clinica médica,* 1915, vol. 1, opened at p. 27.

An important account of transfusion in which sodium citrate was used to prevent coagulation. He employed one gram of a 25 per cent citrate solution to a hundred grams of blood.

82. Weil, Richard. 1876-1917.
Sodium citrate in the transfusion of blood.

Repr.: *Journal of the American medical association,* 1915, vol. 64, p. 425.

An account of Weil's experiments with sodium citrate.

83. Lewisohn, Richard. 1875-
A new and greatly simplified method of blood transfusion.

In: *Medical record,* 1915, vol. 87, p. 141.

An account of the experiments of this American physician who helped to introduce in this country the use of sodium citrate as an anticoagulant. He reached the conclusion that the amount of sodium necessary is only 0.2 per cent. His work was done independently of Hustin, Agote and Weil.

84. Unger, Lester Jarecky. 1888-
A new method of syringe transfusion.

In: *Journal of the American medical association,* 1915, vol. 64, p. 582.

A modification of the syringe method in which a continuous injection of salt solution is made to prevent clotting. An ether spray keeps the syringe cool. (See his article in this same journal for September 18, 1915).

85. Rous, Francis Peyton. 1879-
& Turner, Joseph Richard. 1889-
The preservation of living red blood cells in vitro.

In: *Journal of experimental medicine,* 1916, vol. 23, opened at pp. 246-247.

This important work suggests the addition of glucose and sodium citrate for the preservation of blood cells.

86. Robertson, Oswald Hope. 1886-
A method of citrated blood transfusion.

In: *British medical journal,* 1918, vol. 1, p. 477.

It was largely through Robertson's work that the citrate method of transfusion was introduced to the armies abroad during the World War.

87. Isohemagglutination. Recommendation that the Jansky classification be adopted for universal use.

In: *Journal of the American medical association,* 1921, vol. 76, p. 130.

The confusion arising from the fact that both the Moss and Jansky classifications were in use at the same time, led to the appointment of a special committee to consider the matter. The members of the committee, representing the American Association of Immunologists, the Society of American Bacteriologists and the Association of Pathologists and Bacteriologists, unanimously recommended that the Jansky classification be adopted for universal use, solely on the basis of its priority.

88. Landsteiner, Karl. 1868-
The human blood groups.

In: *Newer knowledge of bacteriology and immunology . . .* (Jordan and Falk), [1928], p. 892.

In spite of the recommendation that the Jansky classification should be used universally, many institutions continued to use the Moss classification. Landsteiner suggests that the groups be designated by the letters O, A, B, and AB, a classification later adopted as the "international classification."

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3. Brown, Horace Manchester. 1858-1929. The beginnings of intravenous medication. In: *Annals of medical history,* 1917, vol. 1, pp. 177-197.
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7. Harper, John. 1890- The international classification of blood groups. In: *U. S. naval medical bulletin,* 1928, vol. 26, pp. 603-606.
8. Herr, Edward Albert. 1883- Blood transfusion to date. In: *Surgery, gynecology and obstetrics,* 1925, vol. 41, pp. 513-520.
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11. Kerr, William Murray. 1880- A history of blood transfusion. In: *U. S. naval medical bulletin,* 1922, vol. 16, pp. 465-475.
12. Keynes, Geoffrey Langdon. 1887- Blood transfusion. London, [1922].
13. McClure, Roy Donaldson. 1882- History of transfusion of blood . . . In: *Journal of the Michigan state medical society,* 1917, vol. 16, pp. 178-184.
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16. Oré, Pierre Cyprien. Études historiques . . . sur la transfusion du sang. 2 ed. Paris, 1876.
17. Prewitt, Theodore Frelinghuysen. 1832-1904. Transfusion—its history and present status. In: *St. Louis medical and surgical journal,* 1876, n.s., vol. 13, pp. [169]-188.
18. Scheel, Paul. 1773-1811. Die transfusion des Blutes . . . Copenhagen, 1802.
19. Snethlage, Rudolf Abraham Iduard. *Bijdrage tot de geschiedenis der Transfusio sanguinis. Amsterdam, 1876.
20. Ullersperger, Johann Baptist. 1798-1878. Prize essay. Ancient transfusion and infusion compared with modern . . . translated by Charles F. Wittig . . . In: *Transactions of the Medical society of the state of Pennsylvania,* 1865, vol. 17, pp. [385]-460.
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* Inaugural dissertation.

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Therapeutic application of female sex hormones	Elmer L. Sevringhaus
Physiology and principal inter-relations of the thyroid	David Marine
Hypothyroidism	J. H. Means
Hyperthyroidism	Harold Thomas Hyman
Surgical treatment of hyperthyroidism and other diseases of the thyroid	Frank H. Lahey
The adrenal medulla	Walter B. Cannon
Adrenal insufficiency	Robert F. Loeb
The adrenal cortex	C. N. H. Long
The Cushing syndrome. Neoplasms of the adrenal gland	B. S. Oppenheimer
Overfunction of the adrenal cortex	Hugh H. Young
Relation of diabetes to the endocrine system	Rollin T. Woodyatt
The influence of the central nervous system upon endocrine activity	J. F. Fulton
Physiology and pathology of parathyroids	William G. MacCallum
Hyperparathyroidism	Henry L. Jaffe
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